Atherosclerosis as a Potential Cause of Deep Embolic Stroke of Undetermined Source: A 3T High-Resolution Magnetic Resonance Imaging Study

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BACKGROUND: The potential causes or sources of embolic stroke of undetermined source (ESUS) vary. This study aimed to investigate the main cause of deep ESUS by evaluating nonstenotic intracranial atherosclerotic plaque.

METHODS AND RESULTS: We retrospectively screened consecutive patients with unilateral anterior circulation ESUS. After excluding the patients with possible embolism from an extracranial artery such as aortic arch plaque, carotid plaque, and so on, the enrolled patients with ESUS were categorized into 2 groups: deep ESUS and cortical with/without deep ESUS. All patients underwent intracranial high-resolution magnetic resonance imaging to assess the characteristics of nonstenotic intracranial atherosclerotic plaque. Biomarkers of atrial cardiopathy (ie, P-wave terminal force in lead V1 on ECG, NT-proBNP [N-terminal pro–brain natriuretic peptide] and left atrial diameter) were collected. A total of 155 patients with ipsilateral nonstenotic intracranial atherosclerotic plaque were found, with 76 (49.0%) in deep ESUS and 79 (51.0%) in cortical with/without deep ESUS. We found more prevalent plaque in the M1 segment of the middle cerebral artery and the ostia of the perforator, with a smaller remodeling index plaque burden, and less frequent occurrence of complicated plaque in deep ESUS versus cortical with/without deep ESUS. Higher BNP (brain natriuretic peptide) levels and a higher prevalence of atrial cardiopathy in cortical with/without deep ESUS versus deep ESUS. Moreover, the discrimination of vulnerable plaque for predicting ESUS was significantly enhanced after adjusting for or further excluding patients with deep ESUS.

CONCLUSIONS: The current study provides the first high-resolution magnetic resonance imaging evidence that cortical with/without deep ESUS and deep ESUS should be 2 distinct entities and that atherosclerosis, not embolism, might be the main cause of deep ESUS.

Key Words: deep embolic stroke of undetermined source ■ high-resolution magnetic resonance imaging ■ nonstenotic intracranial atherosclerotic plaque

The concept of embolic stroke of undetermined source (ESUS) was proposed to capture a specific subtype of stroke requiring more extensive workup to guide future clinical trials.1 For example, 2 major global trials (NAVAGATE-ESUS [New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source], RESPECT-ESUS [Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source]) were performed based on the presumption of a more plausibly favored response to anticoagulation derived from the initial perception with more subclinical atrial fibrillation detected.2–3 However, the neutral results have
CLINICAL PERSPECTIVE

What Is New?
• There are distinct characteristics of intracranial plaque such as plaque distribution, remodeling index and plaque burden, and atrial cardiopathy in deep versus cortical with/without deep embolic stroke of undetermined source.

What Are the Clinical Implications?
• Our findings suggest that cortical with/without deep embolic stroke of undetermined source and deep embolic stroke of undetermined source should be 2 distinct entities and that atherosclerosis, not embolism, might be the main cause of deep embolic stroke of undetermined source.

Nonstandard Abbreviations and Acronyms

| AC | atrial cardiopathy |
| BAD | branch atheromatous disease |
| DPS | discontinuity of plaque surface |
| ESUS | embolic stroke of undetermined source |
| IPH | intraplaque hemorrhage |
| MCA | middle cerebral artery |
| MLN | maximal luminal narrowing |
| NIAP | nonstenotic intracranial atherosclerotic plaque |
| PB | plaque burden |
| RI | remodeling index |

Intracranial atherosclerosis underlying ESUS could be multifactorial and potentially vary from plaque characteristics.17–20 A study from patients with recent stroke in the territory of the middle cerebral artery (>50% stenosis) suggested that cortical/subcortical infarct (artery-to-artery embolic infarct) has distinct vulnerable plaque characteristics compared with deep infarction (nonembolic infarct).21

In this context, we assumed that the heterogeneous characteristics of nonstenotic intracranial atherosclerotic plaque (NIAP) might echo with distinct ESUS subtypes such as deep versus cortical with/without deep ESUS. In the present study, we assessed the characteristics of NIAP in patients with deep versus cortical with/without deep ESUS using 3.0 T HR-MRI to test the hypothesis.

METHODS

The data underlying this article will be shared on reasonable request to the corresponding author.

Study Population
The retrospective study was approved by the Institutional Review Board of the General Hospital of Northern Theater Command (k2019-57), and informed consent was waived. We used the same ESUS cohort that was reported in detail in our recent study.13 Briefly, consecutive patients with acute ischemic stroke in the territory of a unilateral anterior circulation within 1 week from onset to HR-MRI and eligible for proposed diagnostic criteria for ESUS were enrolled between January 2015 and December 2019 in our stroke center. In addition to the diagnostic criteria of ESUS, we further excluded patients with nonstenosing carotid plaque ≥3 mm detected by computed tomography angiography or carotid ultrasonography, aortic arch atherosclerotic plaque with ulceration or ≥4 mm by computed tomography angiography or transesophageal echocardiogram, balloon dilatation and stent, previous radiation therapy to head or neck, and malignant tumor. Therefore, 243 patients with ESUS were included in the present study (Figure 1). More detailed inclusion/exclusion criteria are reported elsewhere.13 Based on the hospital information system, the baseline characteristics were collected, including demographics, medical history and risk factors of cerebrovascular diseases, initial National Institutes of Health Stroke Scale score, and blood investigation results.

Infarct Subtypes
In line with our recent study, according to the topographical locations of infarction (identified by diffusion weighted imaging) and anatomical characteristics of
intracranial arteries, ESUS was categorized into the following 2 types: (1) deep ESUS, which was nonlacunar with a single infarct located only in the basal ganglia and/or lateral ventricle supplied by the lenticulostriate arteries (Figure 2A); and (2) cortical with/without deep ESUS, which included multiple cortical infarcts (at least 2 infarct lesions) or the coexistence of deep and cortical infarctions (Figure 2B).

**Imaging Protocol and Analysis**

The detailed image protocol was reported in our recent study.13 We assessed intracranial vessels, including the cavernous (C3) or supraclinoid (C4) internal carotid artery, the A1 segment of the anterior cerebral artery, and the M1 or the proximal M2 segment of the middle cerebral artery (MCA). A plaque was identified as markedly eccentric or focal wall thickening, with the thinnest wall ≤50% of the thickest part by HR-MRI.22 The culprit plaque was defined as a lesion of ipsilateral proximal vascular territory of infarction with clinical symptoms. The vessel area and luminal area at the maximal luminal narrowing (MLN) site and reference site were measured manually. The plaque at the MLN site was selected in the cross-sectional images of vessels, whereas the reference sites were chosen as the neighboring plaque-free of MLN site or was calculated as the average of the minimal lesion segment proximal and distal to the MLN site because of vessel tapering. Multidimensional parameters were evaluated using 3.0 T HR-MRI, including plaque location, distribution, morphology, and composition.

Plaque location was divided into the cavernous (C3) or supraclinoid (C4) internal carotid artery, the A1 segment of the anterior cerebral artery, the M1 or the proximal M2 segment of the middle cerebral artery (MCA). In the cross-sectional image at the MLN site based on plaque orientation, the plaque distribution was classified into superior, inferior, dorsal, or ventral quadrant of the vessel. A plaque at the ostia of the perforators of M1 of MCA was located at the superior or dorsal quadrant site based on prior documents.23,24 A plaque with circumferential distribution on a quadrant was defined as ≥3 quadrants involved. A plaque opposite the ostia of the perforators was identified as the inferior and/or ventral quadrant.

Plaque morphology involved the remodeling index (RI), plaque burden (PB), and plaque distribution. The RI was defined as the vessel area at the MLN site divided by the reference vessel area. The PB was calculated as (vessel area−luminal area/vessel area at MLN site)×100% (Figure 3).

Plaque components included thick fibrous cap (FC), discontinuity of plaque surface (DPS), intraplaque hemorrhage (IPH), and complicated plaque. The thick FC was defined as a continuous band of a T2 high signal adjacent to the lumen.25,26 DPS was defined as irregularity of the plaque...
luminal surface, such as FC rupture, ulcer plaque, or formation of overlying mural thrombus.\(^{27}\) IPH was defined as a bright T1 signal ≥150% of a T1 signal of an adjacent muscle or pons.\(^{28,29}\) Complicated plaque was defined as any or both of DPS and IPH on the basis of the definition of a complicated American Heart Association type VI plaque.\(^{30}\)

### Biomarkers and Definition of Atrial Cardiopathy

In the present study, atrial cardiopathy (AC) was defined as any or a combined form of P-wave terminal force in lead V1 >4000 \(\mu\)Vxms, NT-proBNP (N-terminal pro–brain natriuretic peptide) >250 pg/mL, and left atrial diameter >3.8 cm for women or >4.0 cm for men. The detailed method of the measurements was reported in our recent study.\(^{31}\)

### Measurement Reproducibility

To assess interobserver and intraobserver variability, the 2 readers (N.L. and Z.-Y.S.) independently re-assessed the infarct subtypes and the plaque parameters at the MLN site of the initial 100 consecutive patients 1 month later.

### Statistical Analysis

We used the Student \(t\) test or Mann–Whitney \(U\) test, as appropriate, for continuous variables and the chi-square test or Fisher exact test for categorical variables to compare the difference of plaque characteristics (location, distribution, morphology, and composition), AC, and AC markers between deep ESUS and cortical +/- deep ESUS. Univariable and multivariable logistic regression analyses were performed to identify whether vulnerable features of plaques were related to the mechanism of the ESUS. Receiver operating characteristic curve analysis of vulnerable features of plaques was performed to evaluate the predictive performance for ESUS. All analyses were performed using SPSS version 22 (GraphPad Software Inc., Prism version 8), and a \(P\) value (2-tailed) <0.05 was considered to indicate statistical significance.
Table 1. Comparison of Demographic Characteristics and Laboratory Examination Between Deep ESUS and Cortical With/Without Deep ESUS

|                | Total (N=243) | Ipsilateral plaque (n=155) | Without ipsilateral plaque (n=88) |
|----------------|---------------|-----------------------------|----------------------------------|
|                | Deep ESUS (n=127) | Cortical +/- deep ESUS (n=116) | P value | Cortical +/- deep ESUS (n=79) | P value | Cortical +/- deep ESUS (n=37) | P value |
| Sex, male      | 76 (59.8)      | 84 (72.4)                   | 0.039 | 60 (50.5)      | 60 (57.5) | 0.039 | 30 (55.8)      | 24 (45.9) | 0.566 |
| Age, y         | 60 (51–66)     | 63 (56–70)                  | 0.001 | 60 (53–69)     | 63 (57–70) | 0.139 | 55 (45–63)     | 63 (55–70) | 0.002 |
| Current smoker | 49 (38.58)     | 40 (32.72)                  | 0.933 | 27 (35.52)     | 44 (55.70) | 0.012 | 22 (43.14)     | 16 (43.24) | 0.992 |
| Alcohol use    | 49 (38.58)     | 47 (40.51)                  | 0.758 | 29 (38.15)     | 29 (36.71) | 0.852 | 20 (39.21)     | 18 (40.65) | 0.378 |
| Hypertension   | 65 (51.18)     | 60 (51.72)                  | 0.933 | 46 (60.53)     | 44 (55.70) | 0.542 | 19 (37.25)     | 16 (43.24) | 0.571 |
| Diabetes       | 28 (22.04)     | 27 (23.27)                  | 0.819 | 21 (27.63)     | 22 (27.85) | 0.976 | 7 (13.73)      | 5 (13.51)  | 0.977 |
| CAD            | 8 (6.29)       | 19 (16.37)                  | 0.013 | 8 (10.53)      | 14 (17.22) | 0.199 | 0 (0.00)       | 5 (13.51)  | 0.007 |
| Prior stroke or TIA | 19 (14.96) | 31 (26.72)                  | 0.023 | 15 (19.74)     | 24 (30.38) | 0.127 | 4 (7.84)       | 7 (18.92)  | 0.121 |
| Initial NIHSS  | 4 (2–8)        | 2 (1–5)                     | <0.001 | 4 (2–8)        | 2 (1–5)    | 0.009 | 5 (2–8)        | 1 (0.5–6.5) | 0.006 |
| Serum urea, mmol/L | 4.93 (4.09–5.89) | 5.41 (4.60–6.67) | 0.006 | 4.76 (4.22–5.90) | 5.52 (4.75–6.77) | 0.006 | 4.99±1.31 | 5.33±1.70 | 0.298 |
| Creatinine, μmol/L | 63.83 (55.04–71.44) | 71.00 (56.06–81.67) | 0.001 | 61.57 (53.11–70.88) | 71.90 (59.90–81.30) | 0.001 | 65.32±14.15 | 69.77±16.59 | 0.180 |
| Homocysteine, μmol/L | 11.66 (9.26–15.70) | 11.63 (8.15–15.58) | 0.906 | 11.66 (9.30–15.28) | 11.66 (9.41–16.00) | 0.720 | 12.32 (8.92–18.83) | 11.52 (8.53–14.91) | 0.470 |
| Total cholesterol, mmol/L | 4.71 (3.84–5.71) | 4.58 (3.76–5.33) | 0.272 | 4.87±1.30 | 4.49±1.04 | 0.048 | 4.73±1.32 | 4.86±1.15 | 0.614 |
| Triglyceride, mmol/L | 1.39 (1.00–2.23) | 1.48 (1.05–1.90) | 0.523 | 1.51 (1.01–2.13) | 1.54 (1.16–1.96) | 0.961 | 1.37 (0.99–2.41) | 1.31 (0.92–1.85) | 0.200 |
| HDL, mmol/L     | 1.02 (0.86–1.19) | 0.97 (0.83–1.12) | 0.131 | 1.01 (0.89–1.19) | 0.92 (0.80–1.09) | 0.035 | 1.02 (0.83–1.19) | 1.08 (0.87–1.19) | 0.688 |
| LDL, mmol/L     | 2.76 (2.08–3.51) | 2.72 (2.17–3.26) | 0.425 | 2.88±0.87 | 2.69±0.80 | 0.151 | 2.76±0.90 | 2.90±0.88 | 0.474 |
| Lipoprotein A, mg/L | 133.20 (82.40–285.80) | 180.35 (96.42–396.22) | 0.065 | 120.55 (81.70–203.88) | 160.80 (85.10–377.30) | 0.128 | 154 (86.00–362.10) | 241.90 (104.85–478.3) | 0.189 |
| Fibrinogen, g/L | 3.17 (2.78–3.69) | 3.35 (2.74–4.02) | 0.092 | 3.15 (2.82–3.76) | 3.33 (2.72–3.87) | 0.473 | 3.12±0.72 | 3.50±0.87 | 0.031 |

Values are mean ± SD, median (interquartile range), or number (percentage). Missing values (9/243) are replaced by the median. CAD indicates coronary artery disease; ESUS, embolic stroke of undetermined source; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.
RESULTS

A total of 587 patients with ESUS were recruited in the initial cohort, and we further excluded patients with bilateral or posterior circulation ESUS (n=193), carotid plaque of ≥3 mm in thickness (n=91), aortic arch atherosclerosis with ulceration or ≥4 mm in thickness (n=15), paradoxical embolism (n=17), patent-foramen ovale (n=10), and poor image quality or incomplete information (n=18). Finally, 243 patients with ESUS (61 years (interquartile range [IQR], 54–68 years)) were enrolled in this analysis, including 155 patients with ipsilateral NIAP and 88 patients without ipsilateral NIAP. Of these patients with ipsilateral NIAP, there were 76/155 patients with deep ESUS and 79/155 patients with cortical with/without deep ESUS with ipsilateral NIAP.

In the patients with ESUS or those with ipsilateral NIAP, patients with deep ESUS were less likely to be men (total: 59.8% versus 72.4%, \(P=0.039\); ipsilateral plaque: 60.5% versus 75.9%, \(P=0.039\)) and had lower serum urea (total: 4.93 [IQR, 4.09–5.89] mmol/L versus 5.41 [IQR, 4.63–6.67] mmol/L, \(P=0.006\); ipsilateral plaque: 4.76 [IQR, 4.22–5.90] mmol/L versus 5.52 [IQR, 4.75–6.77] mmol/L, \(P=0.006\)) and creatinine (total: 63.83 [IQR, 55.04–71.44] μmol/L versus 71.00 [IQR, 59.05–81.67] μmol/L, \(P=0.001\); ipsilateral plaque: 61.57 [IQR, 53.11–70.88] μmol/L versus 71.90 [IQR, 59.90–81.30] μmol/L, \(P=0.001\)) levels than those with cortical with/without deep ESUS. Patients with deep ESUS tended to be younger (total: 60.00 [IQR, 51.00–66.00] years versus 63.00 [IQR, 56.25–69.75] years, \(P=0.001\); ipsilateral plaque: 60.00 [IQR, 53.25–68.75] years versus 63 [IQR, 57.00–70.00] years, \(P=0.139\); without ipsilateral plaque: 55.00 [IQR, 45.00–70.00] years versus 63 [IQR, 59.90–81.30] years, \(P=0.001\)) and had a higher median initial National Institutes of Health Stroke Scale score (total: 4 [IQR, 2–8] versus 2 [IQR, 1–5], \(P<0.001\); ipsilateral plaque: 4 [IQR, 2–8] versus 2 [IQR, 1–5], \(P=0.009\); without ipsilateral plaque: 5 [IQR, 2–8] versus 1 [IQR, 0.5–6.5], \(P=0.006\) and a lower prevalence of coronary artery disease (total: 6.29% versus 16.37%, \(P=0.013\); ipsilateral plaque: 10.53% versus 17.72%, \(P=0.199\); without ipsilateral plaque: 0.00% versus 13.51%, \(P=0.007\)) than those with cortical with/without deep ESUS (Table 1).

There was a significant difference in plaque location and distribution between deep ESUS and cortical with/without deep ESUS (Table 2). In the deep ESUS group, ipsilateral plaque developed more preferably at the MCA M1 segment (82.9% versus 35.4%) and the ostia of the perforator (71.4% versus 17.2%) and had smaller PB (58.85±7.53 versus 68.57±7.41) and RI (1.13 [IQR, 1.04–1.17] versus 1.18 [IQR, 1.16–1.21]) and less frequently occurring complicated plaque (60.5% versus 92.4%), DPS (55.3% versus 91.1%), and IPH (13.2% versus 39.2%) compared with those in the cortical with/without deep ESUS group (all \(P<0.001\)). We also found

| Table 2. Characteristics of Plaque in Patients With Deep Versus Cortical With/Without Deep ESUS With Ipsilateral Plaque |
|---------------------------------------------------------------|
| **Deep ESUS (n=76)** | **Cortical +/− deep ESUS (n=79)** | **P value** |
| Plaque location | | |
| Cavernous (C3), supraclinoid (C4), or terminal segment of ICA | 3/76 (3.9) | 15/79 (19.0) | <0.001 |
| A1 segment of ACA | NA | 10/79 (12.7) | |
| M1 segment of MCA | 63/76 (82.9) | 28/79 (35.4) | |
| M1–M2 or proximal M2 of MCA | 10/76 (13.1) | 26/79 (32.9) | |
| Plaque morphology | | |
| PB, % | 58.85±7.53 | 68.57±7.41 | <0.001 |
| RI | 1.13 (1.04–1.17) | 1.18 (1.16–1.21) | <0.001 |
| Plaque distribution on quadrant | | <0.001 |
| Plaque opposite the ostia of the perforator | 15/74 (20.3) | 32/58 (55.2) | |
| Plaque at the ostia of the perforator | 53/74 (71.4) | 10/58 (17.2) | |
| Circumferential distribution | 6/74 (8.1) | 16/58 (27.6) | |
| Plaque composition | | |
| Complicated plaque | 46/76 (60.5) | 73/79 (92.4) | <0.001 |
| DPS | 42/76 (55.3) | 72/79 (91.1) | <0.001 |
| Thick FC | 31/75 (41.3) | 22/76 (28.9) | 0.111 |
| IPH | 10/76 (13.2) | 31/79 (39.2) | <0.001 |

Values are mean±SD, median (interquartile range), or number (percentage). ACA indicates anterior cerebral artery; DPS, discontinuity of plaque surface; ESUS, embolic stroke of undetermined source; FC, fibrous cap; ICA, internal carotid artery; IPH, intraplaque hemorrhage; MCA, middle cerebral artery; NA, not application; OR, odds ratio; PB, plaque burden; and RI, remodeling index.
that, in the deep ESUS group, ipsilateral plaque developed more preferably at the ostia of the perforator, and contralateral plaques developed more preferably opposite the ostia of perforator ($P<0.001$) (Tables S1).

Compared with patients with deep ESUS, we found that the BNP (brain natriuretic peptide) values and the prevalence of AC were significantly higher in the patients with cortical with/without deep ESUS after excluding the patients with ipsilateral plaque (BNP: $112.40$ [IQR, $47.42–789.80$] versus $433.80$ [IQR, $74.85–1175.50$], $P=0.040$; AC: $87.10\%$ versus $54.90\%$, $P=0.084$; Table S2).

In addition, we analyzed intracranial ipsilateral versus contralateral plaques to ESUS. The univariable logistic regression analyses showed that PB, RI, and complicated plaque were related with an index ESUS (PB [per 0.1 change]: odds ratio [OR], $1.593$ [95% CI, $1.182–2.149$], $P=0.002$; RI [per 0.1 change]: OR, $2.533$ [95% CI, $1.861–3.503$], $P<0.001$; complicated plaque: OR, $2.239$ [95% CI, $1.304–3.845$], $P=0.003$; Table 3). The multivariable logistic analysis showed that RI (RI [per 0.1 change]: OR, $2.295$ [95% CI, $1.661–3.172$]; $P<0.001$), but not PB and complicated plaque (PB [per 0.1 change]: OR, $1.241$ [95% CI, $0.885–1.741$], $P=0.211$; complicated plaque: OR, $1.462$ [95% CI, $0.800–2.671$], $P=0.216$), was related with ESUS. After adjusting for infarction subtypes, larger RI and PB were significantly associated with ESUS (RI [per 0.1 change]: OR, $2.469$ [95% CI, $1.776–3.432$], $P<0.001$; PB [per 0.1 change]: OR, $1.506$ [95% CI, $1.052–2.155$], $P=0.025$; Table 3).

Similarly, after excluding deep ESUS, the vulnerable features (PB [per 0.1 change]: OR, $3.410$ [95% CI, $1.706–6.818$], $P=0.001$; RI [per 0.1 change]: OR, $6.262$ [95% CI, $2.884–13.594$], $P=0.001$; complicated plaque: OR, $5.570$ [95% CI, $1.575–19.696$], $P=0.008$) of ipsilateral nonstenotic intracranial plaque was more prone to be linked to ESUS (Table 3 and Figure 4). In sensitivity analysis, receiver operating characteristic analysis (Figure 5) demonstrated that, when excluding patients with deep infarction, PB was most significantly improved for predicting ESUS in area under the curve (from $0.612$ to $0.761$), followed by RI (from $0.739$ to $0.839$), complicated plaque (from $0.585$ to $0.643$), and IPH (from $0.540$ to $0.601$). The intraobserver and interobserver reproducibility were high for the measurements of RI, PB, presence of DPS, thick FC, and IPH at the MLN site in this cohort (Table S3).

### DISCUSSION

The current study found that there were 2 distinct features between deep ESUS and cortical with/without deep ESUS, including (1) the distinct difference in location and vulnerability of NIAP and (2) the difference in AC-related biomarkers. Furthermore, when further excluding the confounding effect of deep infarction,
Luo et al. Atherosclerosis as the Main Cause of Deep ESUS

The discrimination of biomarkers of plaque vulnerability for predicting ESUS was significantly enhanced. Collectively, these findings suggested that deep ESUS and cortical with/without deep ESUS were 2 distinct entities.

In the current study, we found that (1) more plaques were located at the ostia of the perforator of the MCA M1 in deep ESUS versus cortical with/without deep ESUS; (2) more invulnerable characteristics of ipsilateral NIAP, such as smaller PB and RI, and less frequently occurring complicated plaque were found in deep ESUS versus cortical with/without deep ESUS; and (3) in deep ESUS, ipsilateral plaque developed more frequently at the ostia of perforator, whereas contralateral plaques developed more frequently opposite of the ostia of the perforator. Taken together, the location and characteristics of the ipsilateral NIAP strongly suggested that the cause of atherosclerosis such as BAD, but not embolism, might be the main cause of deep ESUS, which was distinctly different from cortical with/without deep ESUS. BNP was attributed to a nonstenotic plaque occluding the initiation of a perforating branch,15 which was different from the artery-to-artery embolism in ESUS attributed to a plaque rupture or other embolic mechanism.7–13 Thus, a stroke caused by BAD was more likely to be misclassified as ESUS based on the current criteria of ESUS.

As we know, a large, positive remodeling and vulnerable plaque was more likely linked to an embolic stroke, because from the perspective of the potentially biologic mechanisms, an intracranial plaque arose prevalently at opposite the ostia of perforating branches,23,32 where atherosclerotic lesion early originated due to the low wall shear stress, 33 meanwhile, positive remodeling responded to the increased PB leading to high risk of vulnerability to rupture causing embolic stroke.34–36 Plaque developed at the ostia of perforator is likely attributed to a susceptible gene and vascular risk factors.16 But, even a minimal lesion featured by nonremodeling with the least lipid content could considerably increase the risk of proximal perforator artery stenosis or occlusion, and cause a deep and large infarct.37,38

In addition, we found that higher BNP values and a higher prevalence of AC occurred in the cortical with/without deep ESUS versus deep ESUS after excluding the patients with ipsilateral NIAP. On one hand, the results supported our recent findings that AC and ipsilateral NIAP are 2 distinct competing causes of ESUS.31 On the other hand, the results also further...
supported the hypothesis of 2 distinct mechanisms underlying deep ESUS and cortical with/without deep ESUS: the cause of atherosclerosis as a main cause of deep ESUS versus atherogenic and cardiogenic embolism as either cause of cortical with/without deep ESUS.

It is worth noting that ipsilateral NIAP was not found in 40.1% of the deep ESUS cases in the current study, which was beyond our initial expectation. We argue that there are several possible explanations. First, usually only the plaques with >40% PB can be identified by HR-MRI. Thus, some small plaques will be missed. In addition, the plaque without lipid nuclei could mimic a vascular wall, which makes it difficult to distinguish plaques by nonenhanced HR-MRI, but enough to block the perforation.33,37,38 Second, the location of the ostia of the perforator is variable in MCA. Most of the perforator arises along the proximal 17 mm of the MCA,39 but some perforating branches do not arise from the proximal MCA, thus the plaque located in the distal MCA will be missed. Third, some plaques will be missed because of the limitation of the scan thickness of HR-MRI. Fourth, if the plaque obstructs a proximal branch of the MCA,37 it is difficult to discriminate the plaques by the current HR-MRI technique. So we still believe that most of the deep ESUS based on conventional imaging conforms to the earliest ideas proposed by Caplan and belongs to the cause of arteriosclerosis.15

Strengths and Innovations
The strength of this study is that it is the first to determine the multidimensional characteristics of intracranial plaque, including plaque location, morphology, composition, and remodeling pattern in deep versus cortical with/without deep ESUS, and provide strong evidence that BAD may be the main cause of deep ESUS. The findings strongly support that deep ESUS should be ruled out from the family of ESUS, which will enhance the homogeneity of ESUS causes and provide valuable guidance for optimal antithrombotic strategy in patients with ESUS.

Limitations
First, the main limitations of this study are the retrospective nature and the moderate sample size, which could render our conclusions less than definitive, although our strict inclusion–exclusion criteria might maximally limit this effect. Second, the current results support atherosclerosis as the main cause of deep ESUS, but there is a lack of morphological evidence. Third, because of the limitation of HR-MRI used in the present study, some small or early plaques or the plaque occluding distal MCA cannot be identified. In the future, more advanced plaque imaging, for example, 7.0-T magnetic resonance imaging, should be used to further clarify the relationship between BAD and deep ESUS. Finally, further confirmation of these conclusions in a

Figure 5. Comparison of ROC analysis before and after excluding patients with deep ESUS. A, ROC curve analysis of vulnerability of NIAP for predicting ESUS before excluding patients with deep ESUS. B, ROC curve analysis of vulnerability of NIAP for predicting ESUS after excluding patients with deep ESUS. AUC indicates area under the curve; CP, complicated plaque; DPS, discontinuity of plaque surface; ESUS, embolic stroke of undetermined source; IPH, intraplaque hemorrhage; NIAP, nonstenotic intracranial atherosclerotic plaque; PB, plaque burden; RI, remodeling index; and ROC, receiver operating characteristic.
CONCLUSIONS
The present study provided the first HR-MRI evidence supporting the distinct mechanism of deep ESUS versus cortical with/without deep ESUS. Atherosclerosis, not embolism, might be the main cause of deep ESUS. This finding suggested that deep ESUS should be ruled out from the family of ESUS because of the nonembolic mechanism.

ARTICLE INFORMATION
Received May 9, 2022; accepted September 19, 2022.

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Acknowledgments
Author contributions: Luo, Tao, and Shang retrospectively enrolled the patients, acquired the data, and performed the literature search; Luo wrote the article; Luo and Shang performed the statistical analysis; Yang acquired the imaging data; Chen designed the study and critically revised the manuscript; Luo, Shang, Tao, Yang, and Chen approved the content of the article.

Sources of Funding
The work was supported by grants from the Science and Technology Project Plan of Liao Ning Province (2018225023, 2019JH2/10300027). The funding agency had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Disclosures
None.

Supplemental Material
Tables S1–S3

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Table S1. Comparison of ipsilateral vs contralateral plaque features in deep ESUS.

|                          | ipsilateral plaques | contralateral plaques | P     |
|--------------------------|---------------------|------------------------|-------|
|                          | (n=76)              | (n=46)                 |       |
| Plaque location          |                     |                        |       |
| C3, C4 or terminal segment of ICA | 3/76 (3.9)         | 7/46 (15.21)           | 0.028 |
| A1 segment of ACA        | NA                  | NA                     | NA    |
| M1 segment of MCA        | 63/76 (82.9)        | 27/46 (58.69)          | 0.003 |
| M1-M2 or proximal M2 of MCA | 10/76 (13.1)      | 12/46 (26.08)          | 0.072 |
| Plaque morphology        |                     |                        |       |
| PB, %                    | 58.85 ± 7.53        | 59.32 ± 9.33           | 0.758 |
| RI                       | 1.13 (1.04-1.17)    | 1.11 (1.00-1.16)       | 0.024 |
| Plaque distribution on quadrant |                  |                        |       |
| Plaque opposite the ostia of perforator | 15/74 (20.3)    | 30/44 (68.18)          | 0.000 |
| Plaque at the ostia of perforator | 53/74 (71.4)    | 11/44 (25.00)          | 0.000 |
| Circumferential distribution | 6/74 (8.1)       | 3/44 (6.82)            | 0.799 |
| Plaque composition       |                     |                        |       |
| Complicated plaque       | 46/76 (60.5)        | 25/46 (54.35)          | 0.503 |
| DPS                      | 42/76 (55.3)        | 25/46 (54.35)          | 0.922 |
| Thick FC                 | 31/75 (41.3)        | 22/46 (47.83)          | 0.485 |
| IPH                      | 10/76 (13.2)        | 8/46 (17.39)           | 0.523 |

ESUS=embolic stroke of undetermined source; C3= cavernous; C4= supraclinoid; ICA= internal carotid artery; ACA= anterior cerebral artery; MCA=middle cerebral artery; RI= remodeling index; PB= plaque burden; DPS= discontinuity of plaque surface; FC= thick fibrous cap; IPH= intraplaque hemorrhage; Values are mean±SD, median (interquartile range), or /N (%).
Table S2. Comparison of atrial cardiopathy and markers of atrial cardiopathy between deep ESUS and cortical +/- deep ESUS.

|                          | Total (n=243) | ipsilateral Plaque (n=155) | Without ipsilateral Plaque (n=88) |
|--------------------------|---------------|----------------------------|-----------------------------------|
|                          | Deep ESUS     | Non-deep ESUS              | Deep ESUS                         | Non-deep ESUS | P    | Deep ESUS          | Non-deep ESUS          | P    |
|                          | (n=127)       | (n=116)                    | (n=76)                            | (n=79)        |      | (n=51)            | (n=37)              |      |
| BN-proBNP (pg/ml)        | 93.70 (45.62-223.10) | 107.50 (53.67-474.15)      | 89.84 (42.98-185.40)              | 98.62 (44.97-255.40) | 0.084 | 112.40 (47.42-789.80) | 433.80 (74.85-1175.50) | 0.040 |
| Left atrial diameter (mm)| 32.00 (30.00-35.00)  | 63.00 (56.25-69.75)        | 31 (30-34)                        | 32.00 (30.00-34.00) | 0.502 | 33.00 (30.00-36.00)  | 34.00 (31.00-37.00)  | 0.129 |
| PTFV1 (μV*mS)            | 3786.83 (2659.25-4817.26) | 3750.00 (2711.81-5185.33)  | 3368.40 (2080.00-4082.58)         | 2793.82 (2358.21-3907.69) | 0.687 | 4384.91 (3560.44-5325.42) | 5118.13 (4183.60-6689.95) | 0.026 |
| atrial cardiopathy (%)   | 47 (37.00)    | 53 (45.68)                 | 19 (25.00)                        | 26 (32.91)    | 0.170 | 28 (54.90)         | 27 (87.10)          | 0.084 |

ESUS=embolic stroke of undetermined source; NT-proBNP=N-terminal probrain natriuretic peptide; PTFV1=P-wave terminal force in lead V1; Values are mean±SD, median (interquartile range), or n (%);
Table S3. Intraobserver and interobserver reproducibility.

|                           | Intraclass Correlation Coefficient (95% CI) |
|---------------------------|---------------------------------------------|
|                           | Intraobserver                               | Interobserver                             |
| Infarct subtype           | 0.958 (0.937-0.971)                         | 0.930 (0.897-0.953)                       |
| Plaque location           | 0.846 (0.771-0.896)                         | 0.868 (0.803-0.911)                       |
| RI                        | 0.861 (0.793-0.907)                         | 0.838 (0.758-0.891)                       |
| PB                        | 0.831 (0.748-0.886)                         | 0.858 (0.788-0.905)                       |
| Plaque distribution on quadrant | 0.842(0.765-0.894)                      | 0.852(0.779-0.900)                       |
| presence of DPS           | 0.847 (0.781-0.895)                         | 0.871 (0.814-0.912)                       |
| presence of thick FC      | 0.844 (0.775-0.893)                         | 0.865 (0.804-0.908)                       |
| presence of IPH           | 0.927 (0.893-0.950)                         | 0.894 (0.846-0.928)                       |

CI: Confidence interval; PB=plaque burden; RI=remodeling index; DPS=discontinuity of plaque.