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Localization of Infratentorial Lesion could Predict Patent Foramen Ovale as an Etiology in Embolic Stroke of Undetermined Source

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Aim: Embolic stroke of undetermined source (ESUS) is a clinical construct introduced to describe cryptogenic stroke cases with ambiguous diagnoses. Cardiac causes are recognized as a major cause of ESUS, Patent foramen ovale (PFO) being among them. We aimed to investigate the relationship between infarct patterns and PFO in patients with ESUS.

Methods: We evaluated 190 consecutive patients with ESUS registered in the Tokyo Women's Medical University Stroke Registry. Among them, 94 patients who underwent magnetic resonance imaging and angiography, as well as transthoracic and transesophageal echocardiography, were included in this study. The infarct patterns were classified according to location (infratentorial or non-infratentorial lesions), size (small or large infarcts), and number (single or multiple lesions).

Results: Prevalence of PFO was significantly higher in patients in the infratentorial than those in the non-infratentorial lesion group (40.7% versus 14.9%, respectively; $P=0.007$). However, neither lesion size nor number were associated with PFO. In multivariate logistic regression analysis, the presence of infratentorial lesions was independently associated with PFO in ESUS patients (odds ratio: 2.18; 95% confidence interval: 1.24-3.95; $P<0.007$). In 21 patients with PFO, large PFOs were more prevalent in the infratentorial than in the non-infratentorial lesion group.

Conclusions: Infratentorial lesions may be independently associated with PFO in patients with ESUS. The presence of infratentorial lesions could predict the presence of PFO in ESUS cases.

Key words: Patent foramen ovale, Transesophageal echocardiography, Embolic stroke of undetermined source, Acute ischemic stroke, Infratentorial lesion

Introduction

The definition of embolic stroke of undetermined source (ESUS) has recently emerged as a clinical term and presumably designates cryptogenic strokes to embolism with no evidence of lacunar stroke, ipsilateral stenosis in intracranial and extracranial arteries, major cardioembolic sources, or any other definite rate cause[1]. ESUS is a heterogeneous group with multiple potential pathologies as mechanisms of stroke (e.g., several potential embolic sources include minor-risk or covert cardiac sources, veins via paradoxical embolism, and non-occlusive atherosclerotic plaques in the aortic arch, cervical, or cerebral arteries)[1].

Patent foramen ovale (PFO)-associated stroke is widely known as one of the most important causes of ESUS[2]. Previous studies have suggested that large shunts and the presence of concomitant atrial septum aneurysm were associated more with the onset of PFO-related stroke[3, 4]. The detection of PFO is usually confirmed by transesophageal echocardiography (TEE). However, this examination is invasive and may cause discomfort in patients; in other words, TEE cannot necessarily be performed in all patients.

Several studies have reported the relationship between radiological pattern of cerebral infarction; more specifically, studies have demonstrated

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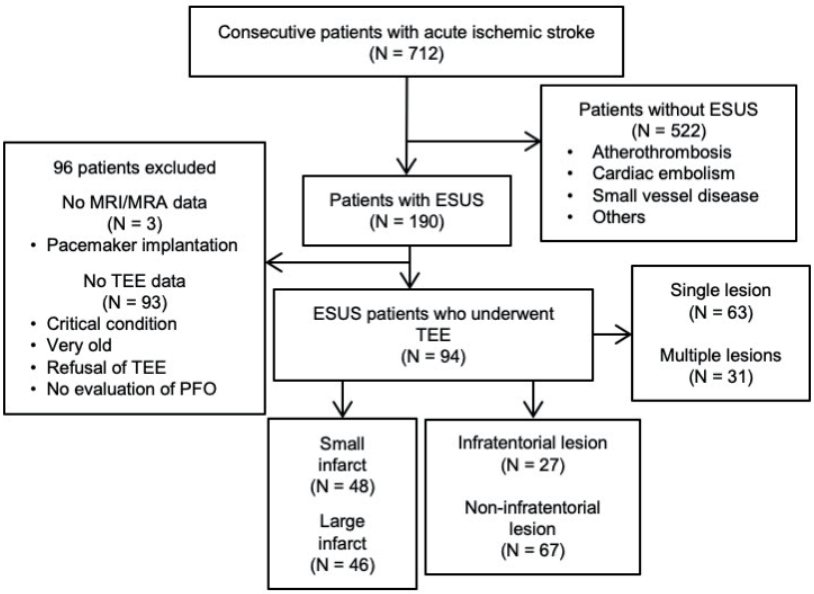

Fig. 1. The flowchart of inclusion and exclusion of patients in the study

N, number of patients; ESUS, embolic stroke of undetermined source; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; TEE, transesophageal echocardiography; PFO, patent foramen ovale.

vertebrobasilar artery territory infarction and PFO in patients with cryptogenic stroke. However, the results have been controversial because cryptogenic stroke includes not only stroke of undetermined cause after comprehensive workup but also stroke with incomplete investigation or due to two or more possible underlying causes. In cases of ESUS, few studies have reported the relationship between radiological patterns of cerebral infarction and PFO-related stroke.

Aim

The aim of this study was to identify the association between infarct patterns and PFO in patients with ESUS.

Materials and Methods

Ethics

The present study conforms to the ethical guidelines of the 1975 Declaration of Helsinki in line with the Ethical Guidelines for Epidemiological Research by the Japanese government and was approved by the ethics committee of Tokyo Women's Medical University Hospital (approval number: 2955-R2).

Study Protocol

Tokyo Women's Medical University Stroke Registry (https://upload.umin.ac.jp, UMIN000031913) is an ongoing, prospective cohort for acute ischemic stroke and transient ischemic attack. All patients gave written informed consent for the inclusion of their data in our study and underwent brain magnetic resonance imaging (MRI) or computed tomography scanning. The present cross-sectional study included 190 consecutive patients with ESUS registered between November 2013 and March 2019. The following patients were, then, excluded: 3 patients who could not undergo MRI and 90 patients who did not receive TEE during hospitalization. In total, 94 ESUS patients who had a complete poststroke workup, including brain imaging, vessel imaging, and extensive cardiac assessments (12-lead electrocardiography, Holter electrocardiography, transthoracic echocardiography, and TEE), were included in the current analysis **(Fig. 1)**. ESUS was defined according to the Cryptogenic Stroke/ESUS International Working Group criteria (i.e., stroke detected by computed tomography or MRI that is not lacunar; absence of extracranial or intracranial atherosclerosis causing ≥ 50% luminal stenosis in arteries supplying the area of ischemia; no major-risk cardioembolic source of embolism or any other specific cause of stroke identified [e.g., arteritis, dissection, migraine or vasospasm, drug misuse, etc.])[1]. The severity of the event was assessed using the National Institutes of Health Stroke Scale (NIHSS) score; NIHSS scores range from 0 to 42,

with higher values reflecting more severe neurologic deficits[5].

Risk Factors

Patients were diagnosed with hypertension if they had evidence of systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or if they had received any antihypertensive medication. Diabetes mellitus was specified as having a fasting serum glucose level ≥ 126 mg/dL, serum glucose level ≥ 200 mg/dL on 2 random measurements, glycated hemoglobin level ≥ 6.5%, or use of antidiabetic therapy (oral hypoglycemic agents or insulin). Dyslipidemia was diagnosed if the patient had low-density lipoprotein cholesterol ≥ 140 mg/dL, total cholesterol ≥ 220 mg/dL, or if the patient had been treated with lipid-lowering agents. The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease formula with the Japanese coefficient. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2. Smoking status was defined based on current use. Intracranial arterial stenosis ≥ 50% on magnetic resonance angiography (MRA), 3-dimensional computed tomography angiography, or digital subtraction angiography was considered a significant finding. Findings of carotid artery ultrasonography were evaluated by trained neurologists, and stenosis ≥ 50% was defined as significant extracranial arterial stenosis.

Blood and Echocardiography Examination

B-type natriuretic peptide (BNP) levels were assessed for all patients on admission.

Transthoracic 2-dimensional and Doppler echocardiography were performed using the iE 33 ultrasound system (Philips Healthcare, Bothell, WA) with an S5 transducer. Left atrial dimension was measured at end-systole when the left atrial chamber was at its greatest dimension. Left atrial enlargement was defined as a left atrial diameter exceeding 4.0 cm in men and 3.8 cm in women[6]. E/e' ratio, which is key parameter for left ventricular diastolic function, was defined as having a cutoff point of 14[7].

The left ventricular ejection fraction was calculated using the biplane Simpson formula. Mitral annulus calcification was defined as an intense echocardiographic-producing structure that was located at the junction of the atrioventricular groove and posterior mitral leaflet on the parasternal long-axis, apical 4-chamber, or parasternal short-axis view[8].

TEE was performed using the Affiniti 30 ultrasound system (Philips Healthcare) using a multiplane probe. Before performing TEE, intraoral xylocaine spray was administered to all patients. The heart rhythm was monitored by electrocardiography during the examination. Patients were placed in the left lateral decubitus position during probe insertion. The probe was advanced to the distal esophagus and withdrawn slowly to a location 40 cm from the incisors. The multiplane probe was manipulated to provide appropriate views, including axial and sagittal images, throughout the aorta. The presence of a right-to-left shunt, such as PFO or pulmonary arteriovenous fistula, was examined by a microbubble study[9]. Briefly, tiny bubbles were formed by shaking sterile salt solution and injecting it into the right antecubital vein. PFO and pulmonary arteriovenous fistula were defined as the appearance of microbubbles in the left atrium within three cardiac cycles or after four cardiac cycles, respectively[10]. The classification of shunt size was based on the number of microbubbles that appeared in the left atrium during the first three cardiac cycles after opacification in the right atrium; the presence of 1 to 5 microbubbles was classified as small PFO, 6 to 25 microbubbles as moderate PFO, and more than 25 microbubbles as large PFO[11]. Atrial septal aneurysm (ASA) is defined as an excursion of the septal tissue (typically the fossa ovalis) of greater than 10 mm from the plane of the atrial septum into the RA or LA or a combined total excursion RA and LA of 15 mm. The aortic arch was observed at 0 and 90 degrees. Mobile plaques were diagnosed as mobile components seen swinging on their peduncles. An ulcerative plaque was diagnosed as a discrete indentation of the luminal surface of the plaque with base width and maximum depth of at least 2 mm each. Complex aortic atheroma was defined as any large plaque greater than or equal to 4 mm in thickness or a plaque with ulceration or mobile components[12]. The examinations were performed and recorded by at least 2 experienced sonographers.

Imaging Examination

All patients underwent brain MRI, including the diffusion-weighted image, apparent diffusion-weighted image, and MRA within 7 days of the onset of stroke. Diffusion-weighted image and MRA results were mandatory for enrollment in the study to confirm an ischemic lesion and to exclude other causes of embolization, respectively. The diffusion-weighted image lesions were analyzed by location, size, and number. Each lesion location was classified into supratentorial, infratentorial, and both regions. The size of each lesion was assessed based on the maximum diameter and divided into one of two groups: small lesion size (those that were smaller than 1.5 cm) and large lesion size (those that were larger than 1.5 cm).

Table 1. Comparison of baseline characteristics between non-infratentorial and infratentorial lesions

Characteristics	Non-infratentorial lesion *N*=67	Infratentorial lesion *N*=27	*P* value
Age, mean ± SD	62.3 ± 13.7	63.5 ± 14.9	0.951
Men, *n* (%)	46 (68.7)	16 (59.3)	0.384
Hypertension, *n* (%)	49 (73.1)	19 (70.4)	0.786
Diabetes Mellitus, *n* (%)	27 (40.3)	13 (48.2)	0.487
Dyslipidemia, *n* (%)	32 (47.8)	13 (48.2)	0.973
Chronic kidney disease, *n* (%)	11 (16.4)	9 (33.3)	0.068
Current smoking, *n* (%)	16 (23.9)	6 (22.2)	0.922
Previous coronary artery disease, *n* (%)	5 (7.5)	2 (7.4)	0.993
Previous cerebral infarction, *n* (%)	11 (16.4)	6 (22.2)	0.456
NIHSS on admission, median (IQR)	1 (1–2)	1 (0–4)	0.041
Anti-thrombotic usage, *n* (%)	18 (26.9)	9 (33.3)	0.531
BNP, pg/mL (IQR)	33.9 (17.6-77.5)	32.2 (15.8-92.4)	0.844
LAD enlargement, *n* (%)	19 (28.4)	5 (18.5)	0.322
Ejection fraction, mean ± SD	55.6 ± 6.1	56.0 ± 3.4	0.806
Mitral valve calcification, *n* (%)	16 (23.9)	8 (29.6)	0.636
LAVI, mean ± SD	31.1 ± 9.8	32.2 ± 11.6	0.709
E/e' ratio >14	10 (14.9)	10 (37.0)	0.022
Left atrial appendage flow	64.1 ± 22.1	68.0 ± 18.5	0.452
Complex aortic atheroma, *n* (%)	13 (19.4)	8 (29.6)	0.362
Atrial septal aneurysm	3 (11.1)	2 (3.0)	0.112
Total PFO, *n* (%)	10 (14.9)	11 (40.7)	0.007
Small/Moderate PFO, *n* (%)	8 (11.9)	3 (11.1)	0.910
Large PFO, *n* (%)	2 (3.0)	8 (30.0)	<0.001

N, total number of patients; SD, standard deviation; *n*, number of patients; NIHSS, National Institute of Health Stroke Scale; IQR, interquartile range; LAD, large atrial diameter; LAVI, left atrial volume index; PFO, patent foreman ovale

The number of ischemic lesions was characterized as single (cortical or subcortical) or multiple (small and scattered in 1 vessel territory, confluent lesion with additional lesions, or multiple vascular territories).

RoPE Score

The Risk of Paradoxical Embolism (RoPE) score was used to differentiate between patients with a high probability of a stroke-related PFO versus an incidental PFO[13]. In stroke patients with PFO and a RoPE score >5 points, the PFO-attributable fraction of stroke risk is 62% or more[13]. Therefore, analyses were performed with stroke patients with PFO dichotomized into the RoPE score >5 and ≤ 5, and compared the relationship between RoPE score and lesion location, size, and number.

Statistics Analysis

Statistical significance of intergroup differences was assessed using the χ^2 test for categorical variables and Student's *t* test or Mann–Whitney *U* test for continuous variables. To identify predictors of the infarct lesion, we performed multiple logistic regression analysis based on a stepwise method with adjustments for age, gender, and other variables with a *P* value <0.20 in univariate analysis as follows: chronic kidney disease, NIHSS on admission, E/e' ratio >14, and PFO. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. In all analyses, a *P* value <0.05 was considered statistically significant.

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Results

Comparison of patient characteristics and PFO between infratentorial lesion and non-infratentorial lesion groups are shown in **Table 1**. The median NIHSS score (1 [interquartile range, 0–4] versus 1 [interquartile range, 1–2], respectively; *P*=0.041) and an E/e' ratio of >14 (37.0% versus 14.9%, respectively; *P*=0.022) were higher in patients of the infratentorial lesion group than in those of the non-

Table 2. Comparison of baseline characteristics between small and medium/large infarcts

Characteristics	Small infarct *N*=48	Large infarct *N*=46	*P* value
Age, mean ± SD	63.0 ± 14.2	61.6 ± 13.8	0.663
Men, *n* (%)	31 (64.6)	31 (67.4)	0.774
Hypertension, *n* (%)	35 (72.9)	33 (71.7)	0.899
Diabetes Mellitus, *n* (%)	24 (50.0)	16 (34.8)	0.136
Dyslipidemia, *n* (%)	24 (50.0)	21 (45.7)	0.673
Chronic kidney disease, *n* (%)	12 (25.0)	8 (17.4)	0.368
Current smoking, *n* (%)	8 (17.0)	14 (33.3)	0.075
Previous coronary artery disease, *n* (%)	5 (10.4)	2 (4.4)	0.255
Previous cerebral infarction, *n* (%)	47 (21.3)	46 (15.2)	0.449
NIHSS on admission, median (IQR)	1 (0–2)	2 (1–3)	0.015
Anti-thrombotic usage, *n* (%)	17 (35.4)	10 (21.7)	0.143
BNP, pg/mL (IQR)	33.3 (17.7-89.3)	33.6 (16.5-76.3)	0.745
LAD enlargement, *n* (%)	15 (31.3)	9 (19.6)	0.194
Ejection fraction, mean ± SD	55.5 ± 4.6	56.0 ± 6.3	0.651
Mitral valve calcification, *n* (%)	12 (25.0)	11 (23.9)	0.912
LAVI, mean ± SD	31.6 ± 11.6	31.2 ± 8.5	0.856
E/e' ratio >14	13 (27.1)	7 (15.2)	0.110
Left atrial appendage flow	53.8 ± 13.4	60.7 ± 16.0	0.029
Complex aortic atheroma, *n* (%)	9 (18.8)	12 (26.1)	0.387
Atrial septal aneurysm	4 (8.3)	1 (2.2)	0.183
Total PFO, *n* (%)	13 (27.1)	8 (17.4)	0.257
Small/Moderate PFO, *n* (%)	7 (14.6)	4 (8.7)	0.375
Large PFO, *n* (%)	6 (12.5)	4 (8.7)	0.550

N, total number of patients; SD, standard deviation; *n*, number of patients; NIHSS, National Institute of Health Stroke Scale; IQR, interquartile range; LAD, large atrial diameter; LAVI, left atrial volume index; PFO, patent foreman ovale

infratentorial lesion group. The prevalence of chronic kidney disease tended to be higher in patients of the infratentorial group than in those of the non-infratentorial group (33.3% versus 16.4%, respectively; $P=0.068$). There was no difference in the prevalence of complex aortic atheroma between the non-infratentorial lesion and infratentorial lesion groups (19.4% versus 29.6%; $P=0.362$). One patient with non-infratentorial lesions had both PFO and complex aortic atheroma, whereas, in patients with infratentorial lesions, no patient had both PFO and complex aortic atheroma. The prevalence of PFO (40.7% versus 14.9%, respectively; $P=0.007$), especially large PFO (30.0% versus 3.0%, respectively; $P<0.001$), was significantly higher in patients of the infratentorial lesion group than in those of the non-infratentorial lesion group.

Comparison of patient characteristics and PFO between small infarct and medium/large infarct are shown in **Table 2**. Median NIHSS on admission (2 [interquartile range, 1–3] versus 1 [interquartile range, 0–2], respectively; $P=0.015$) and left atrial appendage flow (53.8 ± 13.4 cm/s versus 60.7 ± 16.0 cm/s, $P=0.029$) were significantly higher in patients with large infarcts than in those with the small infarcts group. There was no difference in the prevalence of PFO between the two groups (27.1% versus 17.4%, respectively; $P=0.06$).

Comparison of patient characteristics and PFO between single lesion and multiple lesions are shown in **Table 3**. The prevalence of chronic kidney disease was significantly higher in patients of the multiple lesion group than in those of the single lesion group (38.7% versus 12.7%, respectively; $P=0.005$). Furthermore, the prevalence of LAD enlargement was higher in patients of the multiple lesion group than in those of the single lesion group (28.6% versus 39.0%, respectively; $P=0.012$).

Comparison of RoPE score between single lesion and multiple lesions groups showed that the probability of a RoPE score >5 points tended to be higher with multiple lesions than with single lesions (group prevalence, 28.6% versus 14.3%). Comparison of the RoPE score between groups showed that the probability of a RoPE score >5 points tended to be higher with large infarcts than with small infarcts (group prevalence, 37.5% versus 15.4%). Comparison of Rope score between groups showed that the

Table 3. Comparison of baseline characteristics between single and multiple lesions

Characteristics	Single lesion *N*=63	Multiple lesions *N*=31	*P* value
Age, mean ± SD	62.2 ± 14.6	62.5 ± 2.5	0.920
Men, *n* (%)	43 (68.3)	19 (61.3)	0.503
Hypertension, *n* (%)	44 (69.8)	24 (77.4)	0.440
Diabetes Mellitus, *n* (%)	23 (36.5)	17 (54.8)	0.091
Dyslipidemia, *n* (%)	32 (50.8)	13 (41.9)	0.419
Chronic kidney disease, *n* (%)	8 (12.7)	12 (38.7)	0.005
Current smoking, *n* (%)	17 (27.0)	6 (20.0)	0.385
Previous coronary artery disease, *n* (%)	3 (4.8)	4 (12.9)	0.158
Previous cerebral infarction, *n* (%)	11 (17.5)	6 (20.0)	0.767
NIHSS on admission, median (IQR)	1 (0–2)	2 (1–4)	0.120
Anti-thrombotic usage, *n* (%)	17 (27.0)	10 (32.3)	0.597
BNP, pg/mL (IQR)	29.9 (16.0-61.2)	43.2 (21.2-114.6)	0.122
LAD enlargement, *n* (%)	11 (17.5)	13 (41.9)	0.012
Ejection fraction, mean ± SD	56.3 ± 4.6	54.7 ± 6.8	0.205
Mitral valve calcification, *n* (%)	14 (22.2)	10 (32.3)	0.225
LAVI, mean ± SD	30.1 ± 10.1	32.9 ± 10.4	0.406
E/e' ratio >14	10 (15.9)	10 (32.3)	0.052
Left atrial appendage flow	66.0 ± 21.6	63.3 ± 20.3	0.583
Complex aortic atheroma, *n* (%)	11 (18.3)	10 (33.3)	0.113
Atrial septal aneurysm	4 (6.4)	1 (3.2)	0.52
Total PFO, *n* (%)	14 (22.2)	7 (22.6)	0.969
Small/Moderate PFO, *n* (%)	9 (14.3)	2 (6.5)	0.267
Large PFO, *n* (%)	5 (7.9)	5 (16.1)	0.239

N, total number of patients; SD, standard deviation; *n*, number of patients; NIHSS, National Institute of Health Stroke Scale; IQR, interquartile range; LAD, large atrial diameter; LAVI, left atrial volume index; PFO, patent foreman ovale

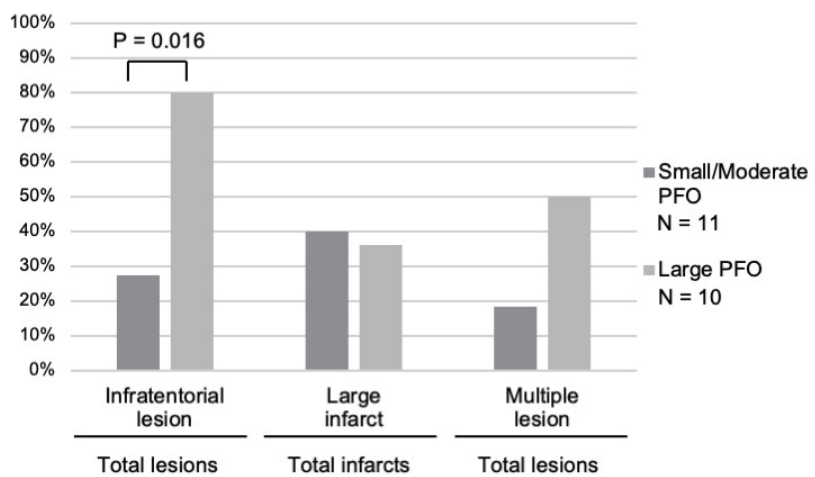

Fig. 2. A comparison of the PFO size and infarct patterns

The presence of large PFO was associated with a higher likelihood of developing an infratentorial lesion than small/moderate PFO. On the other hand, PFO size was not related to lesion size nor lesion number. PFO, patent foramen ovale.

probability of a RoPE score >5 points tended to be higher in the infratentorial lesion group than in the non-infratentorial lesion group (group prevalence, 36.4% versus 10%).

Comparison of PFO size (large or small/moderate PFO) with infarct location, size, and number are shown in Fig. 2. The prevalence of infratentorial lesions was higher in large PFO than in

Table 4. Multiple logistic regression analysis for prediction of infratentorial lesion pattern

Characteristics	OR (95% CI)	*P* value
Chronic kidney disease	1.60 (0.90–2.86)	0.106
NIHSS on admission	1.16 (0.98–1.42)	0.124
E/e' ratio >14	1.89 (1.04–3.46)	0.037
PFO	2.16 (1.23–3.89)	0.008

OR, odds ratio; CI, confidence interval; IQR, interquartile range; PFO, patent foramen ovale

small/moderate PFO (80.0% versus 20.0%, respectively; $P=0.016$). However, there was no relationship between PFO size and infarct size or number. In contrast to PFO, presence of complex aortic atheroma was not related to infarct size, location, or number **(Tables 1, 2, and 3)**. Multivariate logistic regression analysis **(Table 4)** demonstrated that the prevalence of PFO was an independent predictor of location in the infratentorial lesion (OR, 2.16; 95% CI, 1.23-3.89; $P=0.008$).

Discussion

After adjustment for possible confounding factors, infratentorial lesion was associated with the presence of PFO in patients with ESUS. We further showed that large PFO was associated with a higher likelihood of developing infratentorial lesion than small/moderate PFO. Regarding lesion size, left atrial appendage flow velocity was significantly lower in patients with small lesions than in those with large lesions via univariate analysis, although the difference became non-significant after multivariate adjustments. On the other hand, the number of lesions was not associated with baseline characteristics nor echocardiographic findings.

Identifying etiologies of ESUS should be important in determining secondary prevention strategies because several types of potential sources of embolism are established with ESUS. Among them, PFO-related stroke is one of the most important causes in patients with ESUS. Thus far, some studies have investigated the associations of infarct patterns and PFO-related stroke among patients with cryptogenic stroke. For example, Thaler *et al.* explored whether there are radiological variables that are associated with PFO in patients with cryptogenic stroke according to the TOAST classification. They described that large and superficially located strokes, which were defined as involving the cerebral or cerebellar cortex, were likely to be PFO-associated[14]. Furthermore, Kim *et al.*'s research targeted PFO-associated stroke among patients with cryptogenic stroke and investigated the characteristics of lesion pattern by MRI to compare them with atrial fibrillation-associated stroke. They defined cryptogenic stroke in accordance with the TOAST classification or as highly suspicious of cryptogenic embolic source. They identified that PFO-associated stroke was more frequently observed as single cortical infarctions (34.2% versus 3.1%; $P<0.001$) or multiple small (<15 mm) scattered lesions in the same territory (23.1% versus 5.9%; $P<0.001$) and in the vertebrobasilar artery territory (44.4% versus 22.9%) than atrial fibrillation-associated stroke[15]. He *et al.* also demonstrated that PFO-related strokes in cryptogenic stroke patients were observed as having posterior circulation and a small size (<10 mm)[16]. They defined cryptogenic stroke as having a stroke without a confirmed reason after thorough work-up. Cerebral infarctions in the PFO group were located more in the posterior circulation (42.3%), whereas most lesions in the negative PFO group were located in the anterior circulation (59.7%, $P<0.01$). Concerning lesion size, the proportion of patients with small lesion size (<10 mm) was much higher in the PFO group (76.6%) than in the negative PFO group (48.8%, $P<0.001$). The findings of these studies that PFO-related stroke is more frequently observed in the vertebrobasilar artery territories concur with our results. On the other hand, Jauss *et al.* could not indicate the features of neuroimaging in 73 subjects with PFO-associated stroke and cryptogenic stroke without PFO. They defined cryptogenic stroke as having no evidence of carotid stenosis, other apparent stroke causes such as dissection, vasculitis, or an apparent embolic source (atrial fibrillation, aortal plaques, dilated ventricle, other cardiac embolic sources, etc.). Furthermore, they excluded patients whose work-up data were incomplete. The results indicated that it was not possible to discriminate between cryptogenic stroke and stroke from an assumed PFO-associated stroke[17].

Such discrepancy might be partly explained by the usage of different criteria for cryptogenic stroke by study. The reason for this may be due to the fact that no generally accepted definition exists for cryptogenic stroke. ESUS is a clinical construct that can eliminate

this problem because of established diagnostic criteria, and our study is one of the few studies that attempt to identify the relationship between neuroimaging and presumed PFO-associated stroke in patients with ESUS.

Several mechanisms by which PFO-related strokes are frequently located in infratentorial lesions have been suggested. The relationship between infratentorial lesion and PFO-associated stroke is still not completely understood, although several mechanisms have been suggested. A previous study using radionuclide venography revealed excess flow to the vertebrobasilar circulation after the Valsalva maneuver in patients with PFO[18]. Because paradoxical embolisms also need the right-to-left shunt (RLS) to be opened by the Valsalva maneuver, the increased blood flow to the pertinent territory after the maneuver may explain the high incidence of ischemic lesions in the vertebrobasilar circulation in PFO-associated stroke. Vertebrobasilar circulation receives less adrenergic innervation[19]. When the sympathetic tone is increased by the Valsalva maneuver, vertebrobasilar circulation, which is less responsive to sympathetic stimuli, increases blood flow. This may increase the likelihood of blood clot formation after increased blood flow to the vertebrobasilar circulation after passage through the PFO. Hayashida *et al.* used (99m)Tc-MAA to monitor the passage of blood flow through the PFO, and they found that posterior circulation exceeds anterior circulation by 16.1% under the Valsalva maneuver[18].

There are some limitations in this study. First, our study was conducted in a single-center setting and had relatively lower power. Second, since the study excluded 96 patients among 190 patients, it could have potentially led to selection bias. This was primarily because elderly patients, those who had severe neurologic symptoms, or those who died of index stroke acutely who could not undergo TEE, might have been excluded from the analysis. Third, the diagnostic workup for the venous thrombosis was not fully investigated. This means our patients with PFO might not have had a paradoxical embolism. However, as far as we have examined, the patients with ESUS who we detected with PFO by TEE did not have other potential causes of stroke. Therefore, it is not a gross over exaggeration to say that their causes were likely due to a paradoxical embolism. Fourth, in our study, all patients who underwent TEE did not necessarily undergo transcranial echocardiography (TCD) to assess RLS. TCD is widely known to be high sensitivity and noninvasive for RLS diagnosis; therefore, it is useful as a screening tool. Although TCD could not be performed for all patients with ESUS in the present study, TEE was performed with high accuracy because systemic sedation was not used, and microbubble testing was conducted three times under the Valsalva maneuver of sufficient intensity. Fifth, although our study suggested that infratentorial lesions are associated with PFO-related strokes, the RoPE score was not particularly high in patients with PFO in the infratentorial lesion group. However, in cases where PFO was detected by TEE, patients underwent adequate examinations to exclude other potential causes of stroke, and we confirmed no apparent cause. Furthermore, the RoPE score is a probability index; thus, low scores cannot exclude with certainty the possibility of PFO-attributable stroke, while higher scores cannot confirm the causative relationship. Further studies involving more patients are needed for verification.

Conclusion

Infratentorial lesion is independently associated with PFO in patients with ESUS. Further multicenter studies involving a larger number of patients are warranted to verify our results.

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None.

Conflicts of Interest

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