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ORIGINAL ARTICLE

How Topographic Diffusion-Weighted Imaging Patterns can Predict the Potential Embolic Source

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Abstract

Purpose To develop an imaging prediction model for patients with embolic stroke of undetermined source (ESUS), we investigated the association of topographic diffusion-weighted imaging (DWI) patterns with potential embolic sources (PES) identified by transesophageal echocardiography.

Methods From a total of 992 consecutive patients with embolic stroke, 366 patients with the ESUS group were selected. ESUS was defined as no atrial fibrillation (Af) within 24h from admission and no PES after general examination. Clinical variables include age (>80years, 70–80 years), sex, vascular risk factors and left atrial diameter >4cm. Age, sex and vascular risk factors adjusted odds ratio of each DWI for the different PESs were calculated. DWI was determined based on the arterial territories. Middle cerebral arteries were divided into 4 segments, i.e., M1–M4. Moreover, M2 segments were subdivided into superior and inferior branches.

Results The 366 patients consisted of 168 with paroxysmal Af (pAf), 77 with paradoxical embolism, 71 with aortic embolism and 50 with undetermined embolism after transesophageal echocardiography. The variables adjusted odds ratio (OR) of internal carotid artery (OR: 12.1, $p=0.037$), M1 (4.2, $p=0.001$), inferior M2 (7.5, $p=0.0041$) and multiple cortical branches (12.6, $p<0.0001$) were significantly higher in patients with pAf. Striatocapsular infarction (12.5, $p<0.0001$) and posterior inferior cerebellar artery infarcts (3.6, $p=0.018$) were significantly associated with paradoxical embolism. Clinical variables adjusted OR of multiple small scattered infarcts (8.3, $p<0.0001$) were significantly higher in patients with aortic embolism.

Conclusion The associations of DWI with different PES have their distinctive characteristics and DWI along with clinical variables may help predict PES in patients with ESUS.

Keywords Diffusion weighted image · Paradoxical embolism · Embolic stroke of undetermined source · Atrial fibrillation

Abbreviations

ACA	Anterior cerebral artery
cAf	Continuous atrial fibrillation
CMB	Cortical multiple branch infarcts
DWI	Topographic diffusion-weighted imaging patterns
ESUS	Embolic stroke of undetermined source
ICA	Internal carotid artery
MCA	Middle cerebral artery
MSS	Multiple scattered small infarcts
NIHSS	National Institutes of Health Stroke Scale
pAf	Paroxysmal atrial fibrillation

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PCA Posterior cerebral artery
PES Potential embolic sources
PFO Patent foramen ovale
PICA Posterior inferior cerebellar artery
RBA Rostral basilar artery
SCA Superior cerebellar artery
SCI Striatocapsular infarction
TEE Transesophageal echocardiography
TTE Transthoracic echocardiography

Introduction

Embolic strokes that cannot be clearly categorized to any established etiology are referred to as embolic stroke of undetermined source (ESUS), which range from 9% to 25% of all ischemic patients [1–3]. Although ESUS may be caused by various underlying potential sources of embolism (PSE), [5–8] currently proposed criteria for the definition of ESUS do not include transesophageal echocardiography (TEE) as the mandatory diagnostic work-up [4]. Thus, the exact constituent of PSE in ESUS has not been well refined [9–11]. We have conducted the prospective registration for consecutive patients with acute ischemic stroke in a single tertiary medical center since January 2010. For patients with embolic stroke in whom underlying PSE was not detected, TEE was applied as exhaustively as possible to identify the aortocardiac source of embolism.

More importantly, patients with ESUS have a considerable rate of annual stroke recurrence of 4–5% [3]. Thus, early detection of underlying potential embolic sources (PES), particularly atrial fibrillation (Af), is crucial for acute treatment and/or secondary prevention. If acute topographic diffusion-weighted imaging patterns (DWI) would be associated with a specific PES, it may help to identify PES in patients with ESUS in addition to various clinical scores. We conducted the present study to identify aortocardiac sources of embolisms and investigated how DWI patterns may be associated with the different PSEs in the consecutive patients with embolic stroke.

Material and Methods

Stroke Registry

We studied patients from the prospective ischemic stroke registry that included all consecutive patients with first ever acute ischemic stroke within 5 days admitted in the tertiary medical institution Kyoto Second Red Cross Hospital between January 2010 and December 2018. Data on admission were prospectively recorded including demographics, cardiovascular risk factors, the NIHSS score, brain MRI and MRA, carotid ultrasonography, transthoracic echocardiography and left atrial diameter. During hospitalization, the stroke mechanism or etiology was investigated as vigorously as possible applying TEE. The use of human subjects for this study has been approved by the institutional review board of Kyoto Second Red Cross Hospital (reference no. Sp2022-15). Because this is a retrospective analysis of a prospectively collected data where the de-identified clinical records were reviewed without any interventions to participants, our institutional review board waived the need for written informed patient consent in this study. Oral informed consent was obtained from all patients on the occasion of registration.

From 2915 patients with acute ischemic stroke, non-embolic stroke patients who were categorized as having large artery atherosclerosis ($n=871$) and small vessel occlusion including branch atheromatous disease ($n=954$) classified based on Trial of Org 10172 in Acute Stroke Treatment (TOAST) were exclude [12]. Large artery atherosclerosis was defined as infarctions caused by extracranial or intracranial atherosclerosis defined as >50% luminal stenosis or occlusion detected by MRA, carotid echography or CT angiography. In the present study, artery to artery embolism is classified as large artery atherosclerosis. Various vasculopathies such as arterial dissection involving proximal vessels ($n=32$) or patients in whom TEE was not performed ($n=66$) were also excluded leaving 992 patients.

Among 992 patients, various PES were identified after general examination including TTE and specific blood tests. When particular causes were not found by general examination, extensive work-up, such as long-term ECG monitoring and TEE were performed. Patients in whom PES was identified after general examination were categorized as the general group and those in whom PES was identified after extensive work-up were categorized as the ESUS group. Of the patients 66 who could not receive TEE were excluded.

Extensive examinations for underlying Prolonged ECG monitoring and echocardiography (PES)

1. Long term ECG monitoring
   Repetitive ECG, inpatient cardiac telemetry monitoring or 24-h Holter monitoring were applied as frequently as possible during hospitalization. Patients in whom Af was found within 24h from admission were diagnosed as continuous Af (cAf) and those found after 24h from admission were diagnosed as paroxysmal Af (pAf).
2. Left atrial diameter
   In the extensive group, left atrial diameter was assessed using two-dimensional echocardiography by TTE [13]. The anteroposterior diameter of the left atrium was measured at the end of left ventricular systole in the parasternal long axis view perpendicular to the aortic root long

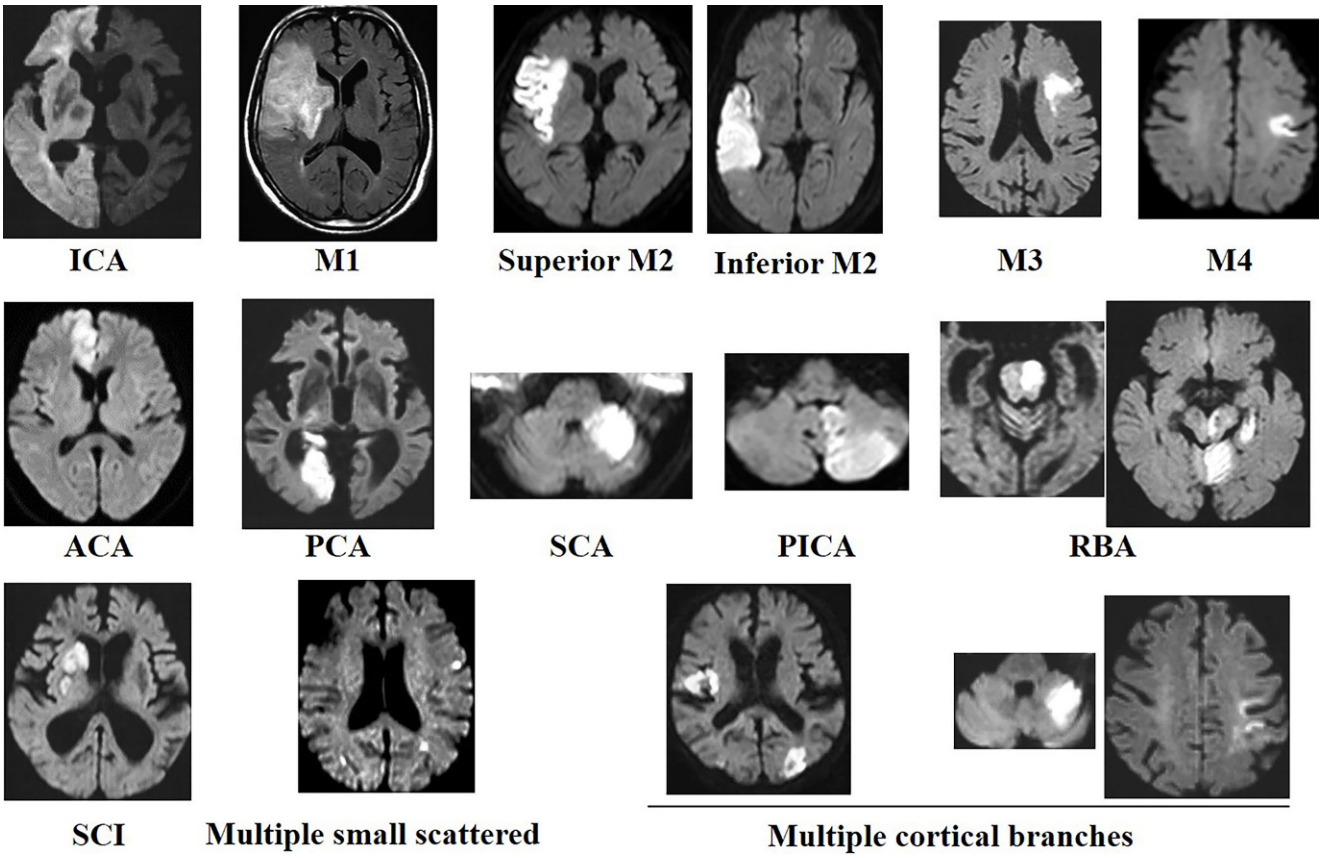

Fig. 1 Typical diffusion weighted image pattern of 14 different vascular territories. *ICA* internal carotid artery, *M1*, *M2*, *M3* and *M4* mean each segment of middle cerebral artery. Superior *M2 M2* superior branch, inferior *M2 M2* inferior branch, *ACA* anterior cerebral artery, *PCA* posterior cerebral artery, *SCA* superior cerebellar artery, *PICA* posterior inferior cerebellar artery, *RBA* rostral basilar artery, *SCI* atriatocapsular infarction. Every sections are axial

axis, and measured at the level of the aortic sinuses by using the inner edge to inner edge convention.

3. Transesophageal echocardiography (TEE)
   A commercially available TEE machine equipped with a multiplane 5-MZ transducer (iE33xMATRIX system, Philips Andover, MA, USA) was used. Paradoxical embolism was defined as embolus carried from the venous side of circulation to the arterial side predominantly via a patent foramen ovale (PFO) detected by TEE. Aortogenic embolism was defined as embolus carried from a vulnerable aortic atheroma detected by TEE [8].
   a. Assessment of aortic atherosclerosis
      The ascending aorta and the aortic arch including the outlet of the left subclavian artery were imaged in short axis and long axis views. Vulnerable aortic arch atheroma was defined as aortic plaques in the ascending aorta or aortic arch that met ≥ 1 of the following criteria: (1) ≥ 4 mm of intima media thickness or (2) ulcerated plaque or (3) mobile plaque [7].
   b. Assessment of PFO
      Using TEE, PFO and atrial septal aneurysm were assessed by an agitated saline contrast study at rest and after Valsalva maneuver. Paradoxical embolism was diagnosed when the passage of > 3 microbubbles to the left atrium within 3 cardiac cycles after complete opacification of the right atrium [8]. Even if the number of bubbles was 1–3, paradoxical embolism was diagnosed when an atrial septal aneurysm defined as ≥ 10 mm of phasic septal excursion into the atrium or venous source of thrombosis were identified [7].

When there were simultaneously two or more possible underlying PES, we arbitrarily prioritized a PES as the following ranking: first pAf, second paradoxical embolism and then aortogenic embolism. Patients in whom no PES was found after TEE were categorized as truly undetermined embolism.

Classification of DWI Patterns

MRI/MRA

MRI scans were performed using 1.5-T superconducting magnets (Gyroscan Intera Achieva 1.5 Pulsar, Philips). Each MRI was performed within 5 days after stroke. Diffu-

sion-weighted scans (TR 1861 ms/TE 69 ms, EPI factor 37) and fluid attenuated inversion recovery (FLAIR) scans (TI 2000 ms,TR 6000 ms, TE 120 ms) were obtained at a slice thickness of 6 mm. Three-dimensional time-of flight images were acquired in the axial plane with a repetition time of 25 ms, echo time of 6.9 ms, flip angle of 18°, 210 mm field of view, partition of 64, 219 512r acquisition matrix and 1 signal average, for a total imaging time of 4 min 33 s. Patients underwent MRI/MRA within 24 h of symptom onset (78%) or between 24h and 72 h after stroke (22%). All MRI scans were assessed by two neurologists (Y.Y. and Y.N.) who were blinded to the clinical findings.

We hypothesized that acute DWI patterns on MRI may depend on characteristic histopathology of thrombi [14–16] and embolic trajectory determined by hydrodynamics [17] that may be associated with the vascular branching pattern. Based on the above, DWI lesion patterns were classified into 14 groups according to the main infarcts based on the dominant arterial territories proposed by Tatu et al. (Figure 1; [19]). The segments of MCA anatomically consisted of M1: horizontal segment, M2: insular segment, M3: opercular segment and M4: cortical segment [20]. The M2 territory was further dichotomized into superior and inferior branches. Thus 14 DWI groups consisted of the territories of (1) ICA, (2) M1, (3) superior M2, (4) inferior M2, (5) M3, (6) M4, (7) multiple lenticurostriate arteries with diameter >20 mm, i.e., striatocapsular infarction (SCI) [20], (8) anterior cerebral artery (ACA), (9) posterior cerebral artery (PCA), (10) superior cerebellar artery (SCA), (11) PICA, (12) rostral basilar artery (RBA) that include rostral pons or midbrain with or without PCA or SCA, (13) multiple cortical branches (MCB) and (14) MSS: multiple scattered small infarcts.

Inferior M2 branch included arteries of posterior parietal, angular, middle temporal, posterior temporal and temporo-occipital, while other branches ascending the parietal lobe were classified as superior M2 branch. The MCB mean at least one cortical infarct and additional cortical or subcortical infarcts in different territory. More than two small infarcts (all of them ≤15 mm) in the different vascular territories were categorized as MSS. Although the SCI can be categorized into M1 occlusion, we separately created this group because a different mechanism can be speculated from infarcts involving cortical area.

Analysis of Data

After describing the characteristics of all patients with embolic stroke, we analyzed patients with the ESUS group in the present study. The concept of the ESUS in the present study was made according to the design of the RESPECT-ESUS [11] because the RESPECT-ESUS included patients with Af that was found after 24h from admission. There is no consensus on the appropriate duration of monitoring after stroke in the ESUS group [12].

Statistical Analysis

Baseline characteristics and DWI patterns were compared between different PES groups setting pAf as reference. Descriptive demographic, clinical, and radiological data are shown as mean ± SD or numbers and frequencies. Discrete variables of ordinal scale were expressed as median and IQR. The χ^2-test, Student's t test or Mann-Whitney test was used as appropriate.

Logistic regression analysis was performed to evaluate the association of acute DWI on MRI with different PES. Additional variables included in this model were age (age 1: 70–80 years vs. <70 years old and age 2: >80 years vs. <70 years old), male sex, vascular risk factors (yes vs. no) and left atrial diameter (≥ 4 cm vs. <4 cm). The OR and 95% CI of each variable and DWI (said pattern vs. the others) for different PES were first calculated as univariate analysis. Then, OR and 95% CI of each DWI for 3 different PESs were calculated after the adjustment of additional variables that were shown to be positive in univariate analysis (Table 3). All statistical analyses were performed using JMP 12 software (SAS Institute Inc., Cary, NC, USA).

Results

Total Patients

Out of 2915 patients with consecutive acute ischemic stroke, 992 patients were diagnosed with embolic stroke (34.0%). PSE was finally identified in 878 patients out of 992 patients with embolic stroke (88.5%). There were 560 patients in the general group and 366 patients in the ESUS group. The general group consisted of 464 patients with cAf, 39 with myocardial infarction, 27 with Trousseau syndrome, 9 with thrombocytosis, 9 with valvular disease and 12 with various causes were identified. The ESUS group consisted of 168 patients with pAf, 77 with paradoxical embolism, 71 with aortogenic embolism and 50 with truly undetermined embolism in whom no PES was identified even after TEE (Table 1).

Analysis in Patients with the ESUS Group

Patients with pAf showed older age and higher score of NIHSS, while those with paradoxical embolism showed younger age and lower prevalence of vascular risk factors. Patients with aortogenic embolism showed male predominance and high prevalence of vascular risk factors. The left atrial diameter was longest in pAf followed by aortogenic

Table 1 Patient characteristics in different embolic source groups in the general group (**a**) and in the ESUS group (**b**)

Potential embolic source	*n*	Age years ± SD	Male	Hypertension	Diabetes mellitus	Hyper-lipidemia	Smoking	Alcohol	National Institutes of Health Stroke Scale	Left atrial diameter (cm)
a										
Continuous atrial fibrillation	464	80.1 ± 9.3	213 (45.9)	351 (75.6)	106 (22.8)	153 (32.9)	61 (13.1)	130 (28.0)	11 (4–20)	–
Myocardial infarction	39	76.3 ± 14.5*	24 (61.5)	26 (66.6)	11 (28.2)	18 (46.1)	12 (30.7)**	10 (25.6)	7 (2–15)	
Trousseau syndrome	27	74.2 ± 10.4***	13 (48.1)	16 (59.2)	5 (18.8)	6 (22.2)	2 (7.4)	8 (29.6)	4 (2–14)*	
Thrombocytosis	9	74.0 ± 16.6	3 (33.3)	8 (88.8)	2 (22.2)	3 (33.3)	1 (11.1)	2 (22.2)	1 (0–16.5)*	
Valvular disease	9	81.8 ± 11.7	1 (11.1)	8 (88.8)	0	4 (44.4)	0	2 (22.2)	6 (1–12)	
b										
Paroxysmal atrial fibrillation	168	80.7 ± 10.1	68 (40.4)	128 (77.5)	26 (15.7)	66 (40.0)	33 (20.6)	47 (30.1)	8 (3–18)	40.0 ± 6.0
Paradoxical embolism	77	65.6 ± 15.0***	41 (54.6)*	40 (52.6)***	0	36 (47.3)	23 (30.6)	30 (40.0)	2 (1–7)***	34.2 ± 6.2***
Aortic embolism	71	76.1 ± 8.3**	53 (74.6)***	62 (87.3)	25 (35.1)***	39 (54.9)	29 (42.0)***	28 (39.4)	3 (1–5)***	37.2 ± 5.8**
Undetermined embolism	50	69.6 ± 12.7***	29 (58.0)*	31 (63.2)	0	18 (36.7)	1 (11.1)	23 (46.9)	3 (1–6)***	36.0 ± 5.3***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, compared with *cAf* in Table 1a and with *pAf* in Table 1b
Numbers and (%)

Table 2 Numbers and percentage of potential embolic sources in different diffusion weighted image patterns

Potential embolic source	*n*	ICA	M1	M2 sup	M2 inf	M3	M4	SCI	ACA	PCA	TOB	SCA	PICA	Po	MCB	MSS
a																
Continuous Af	464	55 (11.8)	109 (23.4)	77 (16.5)	20 (4.3)	11 (2.3)	23 (4.9)	8 (1.7)	3 (0.65)	16 (3.4)	10 (2.1)	11 (2.3)	12 (2.5)	8 (1.7)	80 (17.2)	21 (4.5)
Myocardial infarction	39	1 (2.5)	5 (12.8)	9 (23.8)	0	2 (5.1)	3 (7.6)	4 (10.2)***	0	1 (2.5)	1 (2.5)	0	2 (5.1)	1 (2.5)	7 (17.9)	3 (7.6)
Trousseau syndrome	27	0	0**	4 (14.8)	1 (3.7)	1 (3.7)	1 (3.7)	2 (7.4)*	1 (3.7)	0	0	0	0	0	1 (11.1)	12 (44.4)***
Thrombocytosis	9	0	0	1 (11.1)	1 (11.1)	1 (11.1)	0	0	1 (11.1)	0	0	0	1 (11.1)	0	6 (22.2)	4 (44.4)***
Valvular disease	9	0	1 (11.1)	3 (33.3)	0	1 (11.1)	0	1 (11.1)*	1 (11.1)	0	1 (11.1)	0	0	0	0	1 (11.1)
b																
Potential embolic source	–	ICA	M1	M2 sup	M2 inf	M3	M4	SCI	ACA	PCA	TOB	SCA	PICA	Po	MCB	MSS
Paroxysmal Af	168	11 (6.5)	29 (17.2)	30 (17.8)	10 (5.9)	4 (2.3)	13 (7.7)	0	7 (4.1)	10 (5.9)	5 (2.9)	5 (2.9)	1 (0.6)	0	28 (16.6)	15 (8.9)
Paradoxical embolism	77	1 (1.3)*	4 (5.1)*	7 (9.0)**	0*	2 (2.6)	13 (16.8)	11 (14.2)***	0	9 (11.6)	2 (2.6)	2 (2.6)	7 (9.0)**	–	0**	19 (24.6)***
Aortic embolism	71	0*	1 (1.4) ***	7 (9.8)*	0*	3 (4.2)	4 (5.6)	0	1 (1.4)	9 (12.6)	0	2 (2.8)	3 (4.2)		2 (2.8)**	40 (56.3)***
Undetermined embolism	50	0	3 (12.7)*	8 (16.0)	4 (8.0)	3 (6.0)	7 (14.0)	4 (8.0)***	2 (4.0)	4 (8.0)	1 (2.0)	2 (4.0)	5 (10.0)***		0**	7 (14.0)

ICA internal carotid artery, *M1*, *M2*, *M3* and *M4* mean each segment of middle cerebral artery. superior *M2 M2* superior branch, inferior *M2 M2* inferior branch, *ACA* anterior cerebral artery, *PCA* posterior cerebral artery, *SCA* superior cerebellar artery, *PICA* posterior inferior cerebellar artery, *RBA* rostral basilar artery, *SCI* atriatocapsular infarction
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, compared with *cAf* in Table 2a and with *pAf* in Table 2b.

Table 3 Variables adjusted odds ratio (*OR*), 95% confidential interval (*CI*), *p* value of each DWI pattern for the different PESs in the ESUS Group

	Paroxysmal Af						Paradoxical embolism			Aortic embolism					
	Univariate			Multivariate			Univariate			Univariate			Multivariate		
	OR	95%CI	*p* value	OR	95%CI	*p* value	OR	95%CI	*p* value	OR	95%CI	*p* value	OR	95%CI	*p* value
Age1	4.7	1.9–14.2	0.0004	–			0.2	0.09–0.42	<0.0001	3.6	1.2–15.8	0.016	–		
Age2	12.2	4.9–37.2	<0.0001				0.069	0.028–0.15	<0.0001	2.8	0.92–12.1	0.07			
Sex	0.39	0.25–0.59	<0.0001				1.04	0.62–1.7	0.85	3.3	1.8–6.0	<0.0001			
Hypertension	1.7	1.07–2.7	0.023				0.29	0.17–0.50	<0.0001	3.1	1.5–7.04	0.0008			
Diabetes mellitus	0.54	0.31–0.91	0.021				0.97	0.50–1.8	0.94	2.5	1.4–4.5	0.0015			
Hyperlipidemia	0.77	0.51–1.1	0.23				1.1	0.67–1.9	0.62	1.7	1.02–2.9	0.039			
Smoking	0.51	0.31–0.84	0.0075				1.4	0.80–2.4	0.22	2.3	0.24–0.74	0.0028			
Left atrial diameter ≥ 4	2.5	1.5–4.1	0.0001				0.35	0.17–0.68	0.0014	0.35	0.17–0.68	0.0014			
ICA	13.4	2.5–246.5	0.0007	12.1	1.1–422.1	0.037	0.34	0.01–1.8	0.24	3.60E–07	0.7003	0.021			
M1	4.8	2.2–11.5	<0.0001	4.2	1.7–11.0	0.001	0.44	0.13–1.1	0.1	0.1	0.0057–0.48	0.0013			
M2 superior	1.6	0.93–3.08	0.082	–			0.41	0.16–0.88	0.029	0.43	0.17–0.94	0.036			
M2 inferior	4.3	1.3–19.5	0.013	7.5	1.8–44.9	0.0041	–								
M3	0.56	0.14–1.8	0.34	–			0.78	0.11–3.0	0.76	1.3	0.30–4.8	0.63			
M4	0.58	0.28–1.1	0.13				1.5	0.67–3.2	0.29	0.47	0.13–1.2	0.13			
SCI	3.50E–08	5.08E–59	<0.0001				12.5	4.1–46.3	<0.0001	1.30E–07	1.20E–42	0.01			
ACA	4.7	1.1–31.8	0.027	3.8	0.81–28.1	0.092	3.40E–07	4.60E–35	0.031	0.45	0.024–2.4	0.4			
PCA	0.49	0.21–1.04	0.065	–			1.9	0.82–4.1	0.12	1.7	0.71–3.7	0.21			
RBA	1.9	0.46–9.5	0.36				1.3	0.19–5.8	0.74	3.70E–07	9.20E–18	0.74			
SCA	1.3	0.41–4.9	0.59				0.38	0.02–2.05	0.3	0.38	0.02–2.05	0.061			
PICA	0.076	0.0042–0.36	0.0005				3.6	1.2–10.6	0.018	0.62	0.096–2.3	0.52			
MSS	0.13	0.10–0.34	<0.0001				1.3	0.70–2.3	0.38	8.1	4.6–14.6	<0.0001	8.5	4.3–17.1	<0.0001
MCB	19	5.5–119.0	<0.0001	12.6	3.2–83.8	<0.0001	1.10E–07	4.20E–23	0.0002	0.27	4.20E–23	0.0002	–		

ICA internal carotid artery, *M1*, *M2*, *M3* and *M4* mean each segment of middle cerebral artery. superior *M2 M2* superior branch, inferior *M2 M2* inferior branch, *ACA* anterior cerebral artery, *PCA* posterior cerebral artery, *SCA* superior cerebellar artery, *PICA* posterior inferior cerebellar artery, *RBA* rostral basilar artery, *SCI* atriatocapsular infarction

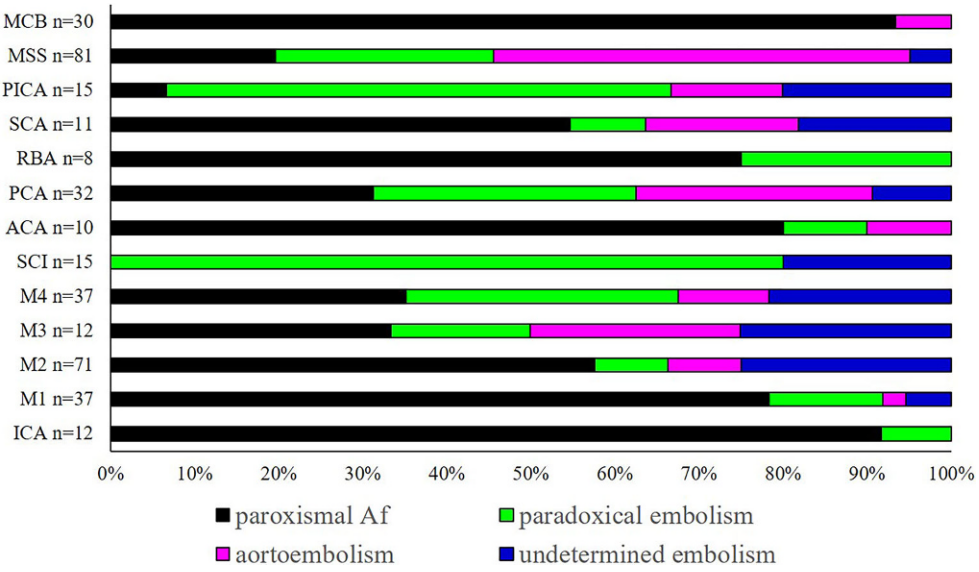

Fig. 2 The percentage of potential embolic sources in each of diffusion weighted image pattern in patients with the ESUS group

embolism and shortest in paradoxical embolism (Table 1b; [20]).

Comparison was made setting pAf as a reference in individual DWI of the total 14 DWI groups. In the DWI of M1, superior M2, inferior M2 and MCB, the prevalence of paradoxical embolism and aortogenic embolism were significantly lower than pAf. In SCI and PICA, paradoxical embolism was significantly higher than pAf. In MSS, paradoxical embolism and aortogenic embolism were significantly higher than pAf (Table 2b). The percentage of different PES in each DWI is depicted in Fig. 2.

Logistic regression analysis of individual DWI pattern for 3 different PES was performed as follows:

1. For pAf
   Variables that showed positively significantly high ORs for pAf by univariate analysis were age 1 (4.7, $p=0.0004$), age 2 (12.2, $p<0.0001$), hypertension (1.7, $p=0.023$) and left atrial diameter ≥ 4 cm (2.5, $p=0.0001$). After adjustment of such variables, the DWI of ICA (12.1, $p=0.037$), M1 (4.2, $p=0.001$), inferior M2 (7.5, $p=0.0041$) and MCB (12.6, $p<0.0001$) were independently associated with pAf. ACA showed close to significant difference.
2. For paradoxical embolism
   There were no variables that showed positively significantly high ORs for paradoxical embolism. The DWI of SCI and PICA showed significantly high ORs (12.5, $p<0.0001$, 3.6, $p=0.018$, respectively).
3. For aortogenic embolism
   Variables that showed positively significant high ORs for aortogenic embolism were age 1 (3.6, $p=0.016$), male sex (3.3, $p<0.0001$), hypertension (1.7, $p=0.023$), diabetes mellitus (2.5, $p=0.0015$), hyperlipidemia (1.7, $p=0.039$) and smoking (2.3, $p=0.0028$). After adjustment of such variables, MSS was independently associated with aortogenic embolism (8.1, $p<0.0001$).

Discussion

The present study identified specific PSE for 88.5% of all patients with embolic stroke.

The associations of each DWI with different PES have their distinctive characteristics in addition to clinical variables and may help in predicting underlying PES in patients with the ESUS group. Prominent characteristics in pAf were high ORs of ICA, M1, inferior M2 and MCB along with high age and large left atrial diameter. Although large infarct volume and MCB in pAf were previously reported as found in the present study, [7, 8] the high prevalence of inferior M2 was a unique finding in this study.

The relationship between pAf and large infarct volume may partly be explained from characteristic histopathology of thrombi [14–17]. The thrombus composition retrieved after thrombectomy revealed AF-related cardioembolic thrombi to be higher proportions of fibrin/platelets, less erythrocytes, and more leucocytes than non-cardioembolic thrombi [14–17]. Erythrocyte-rich areas are entangled in a thin fibrin meshwork, while platelet-rich areas are characterized by dense fibrin structures [17]. As fibrin/platelet-rich thrombi are highly organized and exhibit dense and compact structure, it may cause the occlusion of larger caliber arteries. High prevalence of MCB may be associated with thrombus fragmentation. The degree of inflammatory cell invasion within the thrombus including neutrophil elastase-positive cells [22] or the higher percentage

of lymphocytes [23] were suggested to promote thrombus degradation. Given higher percentages of white blood cells in the thrombus of AF-related cardioembolisms, [14–17] MCB may be naturally associated with pAf.

The present study found inferior M2 was specifically associated with pAF. There were no patients with inferior M2 that were associated with paradoxical embolism or aortogenic embolism. It means inferior M2 infarcts are exclusively caused by pAf-related cardioembolism. The course of emboli is suggested to be determined by the hydrodynamic low or embolus properties [18, 24, 25]. The angular artery that represents the inferior M2 was reported to be the most frequent recipient site of emboli [18]. It could be possible that the agglomerate of fibrin/platelet-rich thrombi associated with pAf may be high density and preferentially flow into the inferior division of M2 branches that may be hydrodynamically less resistant [25]. Embolus trajectory through the branching vessels should be further investigated.

It should also be emphasized that SCI showed a high OR of 12.5 for paradoxical embolism. SCI is mainly caused by MCA embolic occlusion that is succeeded by early recanalization [21]. Venous thromboembolisms that are rich in fibrin and red blood cells may be more easily resolved spontaneously or by thrombolysis than in the case of Af-related cardioembolism [26]. Boutet et al. found paradoxical embolisms more often have subcortical single lesions larger than 15 mm compared with cardiogenic embolisms [27]. Ryoo et al. studied 321 patients with cryptogenic stroke and found subcortical lesions more frequently in paradoxical embolism (58 patients, 37.9%) than in pAf (15 patients, 11.7%) [8]. Such results support our findings. These findings should be further confirmed in a larger cohort study.

In addition to SCI, PICA was significantly associated with paradoxical embolisms. Chung et al. studied 2702 consecutive patients with acute ischemic stroke and found cardioembolism was most frequent in SCA territory infarcts accounting for 60%, while only 15.3% was in PICA infarcts [28]. The prevalence of pAf in SCA (54.5%) and PICA (6.6%) in our study was similar to their findings. It could be possible that highly organized fibrin/platelet-rich thrombi tend to go straight to the basilar top, while fibrin and red blood cell-rich thrombi with light density may hydrodynamically stray into the PICA that branch off forming various angles to the vertebral artery [29]. Patients with paradoxical embolism showed younger age and less vascular risk factors resulting in high RoPE (risk of paradoxical embolism) scores [30].

Most characteristic DWI in aortogenic embolism were MSS. It has consistently been reported that DWI patterns in aortogenic embolisms are characterized by multiple small scattered lesions in multiple vascular territories [31, 32]. Patients with aortogenic embolisms showed older age and preponderance of male sex and various vascular risk factors in line with previous studies [31, 32].

Limitations and Strengths of the Present Study

Limitations should be addressed. The correlation of DWI and PES can result by chance; however, the number is substantial and the correlation of DWI with cAF, which was not a focus of the paper, was similar to that of DWI with pAf. If more than two underlying PES were possible, we prioritized a PES based on an arbitrarily ranking. A strength of this study is applying TEE as exclusively as possible for patients in whom PES was not found after general examination.

In conclusion, the DWI of ICA, M1, inferior M2 and MCB along with older age, large left atrial diameter were independently associated with subsequent pAf. The DWIs of SCI and PICA were significantly associated with paradoxical embolism and that of MSS with aortogenic embolism. The DWI appears to be determined by characteristic histopathology of thrombi and the embolic trajectory is determined by hydrodynamics. Topographic DWI patterns in acute patients may assist with identifying underlying PES in patients with ESUS.

Author Contribution YY contributed to the conception and design of the study. YN, ET, TY, JF and TO contributed to the acquisition and analysis of data. YY and YN contributed to drafting the text or preparing the figures.

Conflict of interest Y. Yamamoto, Y. Nagakane, E. Tanaka, T. Yamada, J. Fujinami and T. Ohara declare that they have no competing interests.

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