

Original Paper

Usefulness of Transesophageal Echocardiography for Predicting Covert Paroxysmal Atrial Fibrillation in Patients with Embolic Stroke of Undetermined Source

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Keywords

Atrial fibrillation · Embolic stroke of undetermined source · Transesophageal echocardiography

Abstract

Background: Covert paroxysmal atrial fibrillation (CPAF) is a major cause of embolic stroke of undetermined source (ESUS). However, detecting PAF during hospitalization in these patients is difficult. **Objectives:** This study aimed to determine whether findings of transesophageal echocardiography (TEE) during hospitalization are associated with later detection of PAF in patients with ESUS. **Method:** We retrospectively studied 348 patients with ESUS who were admitted to our hospital within 1 week of onset. These patients met the criteria of ESUS, underwent TEE during hospitalization, and were followed up for at least 1 year. **Results:** We found PAF in 35 (10.0%) patients. In patients with PAF, spontaneous echo contrast (SEC) and low left atrial appendage flow (LAAF) by TEE and enlargement of the left atrial dimension (LAD) by transthoracic echocardiography were identified more frequently compared with those who did not have PAF. In multivariate analysis, SEC and an LAD ≥ 42 mm were independently associated with later detection of PAF ($p < 0.05$). An association of LAAF < 46.9 cm/s and PAF was marginal ($p = 0.09$). The specificity of the combined finding of SEC and/or LAAF with that of LAD increased up to 90%, while that of LAD alone was 70%. **Conclusions:** The findings of TEE during hospitalization may be useful for identifying patients at increased risk of CPAF in patients with ESUS.

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Introduction

Approximately 25% of all ischemic strokes are cryptogenic [1]. Among them, the clinical entity of embolic stroke of undetermined source (ESUS) has been recently established and is expected to be useful for determining how antithrombotic therapy is performed [1]. However, ESUS is simply defined as nonlacunar brain infarction without proximal arterial stenocclusive lesion or cardioembolic sources. Therefore, ESUS can include heterogenous pathogenesis, such as covert paroxysmal atrial fibrillation (CPAF), minor-risk potential cardioembolic sources, arteriogenic/aortogenic embolism, paradoxical embolism, cancer-associated embolism, and undetermined embolism (unidentified or two potential embolic sources). Therefore, antithrombotic therapy (i.e., anticoagulation or antiplatelet) should be considered on the basis of the individual pathogenesis. An example of this situation is that ESUS with CPAF should be treated with anticoagulants for secondary prevention. However, detecting paroxysmal atrial fibrillation (PAF) during hospitalization is often difficult, even with continuous electrocardiographic (ECG) monitoring. Prolonged rhythm monitoring, including an insertable cardiac monitor, is currently available and may contribute to the detection of PAF [2, 3].

Recent studies have suggested that transesophageal echocardiography (TEE) may be useful for determining the pathogenesis in patients with ESUS [4, 5]. TEE can be used to evaluate plaque formation of the aortic arch, which can cause aortogenic embolism, and the presence of a patent foramen ovale (PFO), which can potentially cause paradoxical embolism. However, PFO is observed in up to 30% of healthy controls [4, 5]. Furthermore, TEE enables evaluation of left atrial function in detail, which cannot be evaluated by transthoracic echocardiography (TTE). Spontaneous echo contrast (SEC), which is an echogenic swirling pattern of blood flow in the left atrium [6], and left atrial appendage flow (LAAF), which is known to be associated with appendage thrombus [7], may be highly associated with left atrial function. Decreased left atrial function may be associated with the presence of atrial fibrillation (AF). Therefore, we hypothesize that abnormal findings of the left atrium as detected by TEE predict the presence of CPAF in patients with ESUS.

In the present study, we retrospectively examined whether TEE findings in patients with the acute phase of ESUS during hospitalization are associated with later detection of PAF in a follow-up of longer than 1 year.

Materials and Methods

This study was approved by our institutional ethics review board. We obtained general written informed consent about the use of clinical data for educations and researches from all patients who were admitted to our hospital for acute stroke, although it was not specific for this study.

Patients

We retrospectively evaluated 1,244 patients who developed ischemic stroke or transient ischemic attack. These patients were admitted to our hospital within 1 week of onset from March 2008 to April 2014. We suspected 732 patients of having embolic stroke because of their symptoms and the site of ischemic stroke, such as sudden onset, and cortical or subcortical lesions. Of these patients, 491 underwent TEE, and 354 patients met the criteria of ESUS proposed by Hart et al. [1]. Finally, 348 patients were followed up for longer than 1 year.

Clinical Assessment

The following cerebrovascular risk factors were investigated: hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, or current treatment with antihypertensive medication), diabetes mellitus (fasting plasma glucose levels ≥ 126 mg/dL or plasma glucose levels ≥ 200 mg/dL at any time, and hemoglobin A_{1c} $\geq 6.5\%$ or current treatment with antidiabetic medication), hypercholesterolemia (serum low-density lipoprotein-cholesterol levels ≥ 3.62 mmol/L or current treatment with antihyperlipidemic medication), end-stage renal failure (creatinine clearance ≤ 15 mL/min), smoking (previous or current cigarette smoking), drinking (current habitual drinking), and a history of stroke and heart disease (ischemic or valvular heart disease).

Echocardiography

TTE and TEE were performed. Data of TTE were obtained using a commercially available ultrasound system (model iU22; Philips, Eindhoven, the Netherlands) equipped with a 2.5-MHz phased array transducer for TTE. Left atrial dimension (LAD) was measured using the M mode or 2-dimensional echocardiography. LAD was measured from the posterior aortic wall to the posterior left atrial wall in the parasternal long axis view at end-ventricular systole [8]. Left ventricular mass was estimated by the Devereux equation. A commercially available real-time 2-dimensional echocardiography system (model iU22; Philips) equipped with a 5.0-MHz phased array omniplane transesophageal transducer was used for TEE. TEE was performed within at least 7 days after onset of stroke. First, the left atrium was observed, and the presence of SEC, thrombus, and valvular strands was assessed. SEC was defined as an echogenic swirling pattern of blood flow in the left atrium at every 0, 30, 60, and 90 degrees, and this was distinct from white noise artifacts [6]. We then measured LAAF and mobility of the atrial septum.

We adopted the lowest value of inflow or outflow velocity as LAAF. Atrial septal aneurysm was defined as ≥ 13 mm of mobility of the atrial septum [9, 10]. The presence of a right-to-left shunt, such as PFO or pulmonary arteriovenous fistula, was then examined by a microbubble study according to recommendations for echocardiography by the European Society of Cardiology [11]. Briefly, tiny bubbles were formed by shaking sterile salt solution and injecting it into an antecubital vein. PFO and pulmonary arteriovenous fistula were defined as appearance of bubbles in the left atrium within 3 heart beats or after 4 heart beats, respectively. Finally, the aortic arch was observed in the transverse and sagittal views. Maximum intima-media thickness >4.0 mm and the presence of ulcerative or mobile plaques were regarded as complex aortic arch atheroma [6].

Follow-Up Examination to Detect PAF

The mean length of stay in hospital for ischemic stroke or transient ischemic attack was 14 days (9–19 days). During hospitalization, ECG monitoring was performed in all patients. Holter ECG was also performed in 97% (337/348 patients) of patients at least once.

Patients were followed up at our outpatient clinic and affiliated primary care physicians' offices approximately once a month after discharge from our hospital. Physicians checked the patients' pulse and asked patients about complaints of palpitations and irregularity of their pulse. Occasional ECG or Holter ECG at a physician's request was performed to detect PAF. We examined whether AF had been detected during follow-up periods from the medical records. "PAF" which we described as the outcome could include CPAF and developing AF, because we could not distinguish these states.

Statistical Analysis

The two-tailed *t* test, Wilcoxon two-tailed test, and χ^2 test were used to compare parameters between patients with and without PAF. A two-tailed $p < 0.05$ was considered to indicate

Table 1. Patients' characteristics

	Total (n = 348)	Paroxysmal atrial fibrillation		p
		detected (n = 35)	not detected (n = 313)	
Age, years	72.2±11.5	75.4±7.2	71.9±11.8	0.09
Men	200 (57.5%)	17 (48.6%)	183 (58.5%)	0.26
Hypertension	271 (77.9%)	29 (82.9%)	242 (77.3%)	0.45
Diabetes mellitus	103 (29.6%)	8 (22.9%)	95 (30.4%)	0.36
Hypercholesterolemia	187 (53.7%)	16 (45.7%)	171 (54.6%)	0.32
End-stage renal failure	19 (5.5%)	3 (8.6%)	16 (5.1%)	0.39
Smoking	174 (50.0%)	13 (37.1%)	161 (51.4%)	0.11
Drinking	140 (40.2%)	15 (42.9%)	125 (39.9%)	0.74
History of heart disease	101 (29.0%)	12 (34.3%)	89 (28.4%)	0.47
History of stroke	68 (19.5%)	5 (14.3%)	63 (20.1%)	0.41
NIHSS score on admission	2 (IQR 0–4)	2 (IQR 0–4)	2 (IQR 0–4)	0.80

NIHSS, National Institute of Health Stroke Scale; IQR, interquartile range. Data for age are shown as means ± SD.

statistical significance. The best cutoff points of LAD and LAAF for predicting PAF were decided by receiver operating characteristic curve analysis retrospectively. We then examined which echocardiographic parameters were associated with the presence of PAF by multivariate analysis. Analyzed parameters included age, sex, hypertension, diabetes mellitus, hypercholesterolemia, end-stage renal failure, smoking, drinking, a history of stroke, a history of heart disease, SEC, LAAF <46.9 cm/s, and LAD ≥42 mm. We created a model of combined parameters using echocardiographic findings with $p < 0.10$ in multivariate analysis and evaluated sensitivity and specificity of the model. The data were analyzed using JMP 12.2.0 software (SAS Institute, Cary, NC, USA).

Results

Patients' Characteristics

A total of 348 patients who were diagnosed with ESUS and underwent TEE were included in this study. The patients' characteristics are shown in Table 1. The mean age of patients was 72.2 ± 11.5 years, and 57.5% were men. The mean follow-up period was 60.0 months (44.0–80.8 months). AF was detected in 35 (10.0%) patients during the follow-up period. Risk factors, a medical history of heart disease and stroke, and the National Institutes of Health Stroke Scale score on admission were not different between patients with and without PAF.

Echocardiographic Findings

Abnormal findings were observed in 291 (83.6%) patients by TEE. Complex aortic arch atheroma was most frequently found, followed by right-to-left shunt, including PFO and pulmonary arteriovenous fistula (Table 2). However, these findings were equally observed between patients with and without PAF. In contrast, SEC was more frequently observed in patients with PAF than in those without PAF ($p < 0.0001$). Furthermore, patients with PAF had significantly lower LAAF than did those without PAF ($p < 0.05$). The best cutoff point of LAAF for predicting PAF was 46.9 cm/s by receiver operating characteristic curve analysis.

Table 2. Echocardiographic findings

	Total (n = 348)	Paroxysmal atrial fibrillation		p
		detected (n = 35)	not detected (n = 313)	
<i>TEE findings</i>				
Complex aortic arch atheroma	213 (61.2%)	25 (71.4%)	188 (60.1%)	0.19
Mobile plaque	23 (6.6%)	4 (11.4%)	19 (6.1%)	0.23
Ulcer	87 (25.0%)	8 (22.9%)	79 (25.2%)	0.76
Patent foramen ovale	50 (14.4%)	2 (5.7%)	48 (15.3%)	0.12
Pulmonary arteriovenous fistula	27 (7.8%)	2 (5.7%)	25 (8.0%)	0.63
Spontaneous echo contrast	36 (10.3%)	11 (31.4%)	25 (8.0%)	<0.0001
Left atrial thrombus	4 (1.2%)	1 (2.9%)	3 (1.0%)	0.32
Atrial septal aneurysm	39 (11.2%)	1 (2.9%)	38 (12.1%)	0.10
Valvular strands	92 (26.4%)	6 (17.1%)	86 (27.5%)	0.19
Left atrial appendage flow, cm/s	67.0 (IQR 51.6–82.3)	56.6 (IQR 32.9–80.7)	67.9 (IQR 53.2–82.3)	0.02
<25.0 cm/s	8 (2.3%)	4 (11.4%)	4 (1.3%)	0.0001
<46.9 cm/s	63 (18.1%)	14 (40.0%)	49 (15.7%)	0.0004
Others	3 (0.9%)	0 (0%)	3 (1.0%)	0.56
No findings	57 (16.4%)	5 (14.3%)	52 (16.6%)	0.72
<i>TTE findings</i>				
Left atrial dimension, mm	38.7±5.9	41.7±4.9	38.3±5.9	0.001
Left ventricular mass index	145.0 (IQR 118.2–174.7)	153.6 (IQR 126.6–184.0)	144.2 (IQR 117.1–174.6)	0.33
Fractional shortening, %	40.9 (IQR 35.4–45.9)	41.0 (IQR 35.7–45.5)	40.9 (IQR 35.2–46.0)	0.89
Ejection fraction	71.0 (IQR 64.0–77.0)	70.0 (IQR 65.0–76.0)	71.5 (IQR 64.0–77.3)	0.65

IQR, interquartile range; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography. Other TEE findings included ventricular septal defect (n = 1), atrial septal defect (n = 1), cardiac tumor (n = 1), Chiari network (n = 1), and right atrial thrombus (n = 1). Data for left atrial dimension are shown as means ± SD.

Table 3. Associations between clinical parameters and detection of paroxysmal atrial fibrillation

	OR	95% CI	p
Left atrial dimension ≥42 mm	3.64	1.64–8.34	0.002
Spontaneous echo contrast	3.60	1.29–9.80	0.01
Left atrial appendage flow <46.9 cm/s	2.27	0.89–5.57	0.09
Age	0.99	0.04–1.03	0.72
Men	1.41	0.46–4.42	0.55
Hypertension	0.62	0.19–1.71	0.37
Diabetes mellitus	1.12	0.45–3.02	0.81
Hypercholesterolemia	1.43	0.64–3.23	0.38
End-stage renal failure	0.48	0.11–2.64	0.37
Smoking	1.99	0.73–5.42	0.18
Drinking	0.59	0.23–1.52	0.28
History of heart disease	1.32	0.54–3.41	0.55
History of stroke	1.64	0.57–5.54	0.37

OR, odds ratio; 95% CI, 95% confidence interval. Left atrial dimension was measured by transthoracic echocardiography, and the other two parameters (spontaneous echo contrast and left atrial appendage flow) were measured by transesophageal echocardiography. Analyzed parameters included age, sex, hypertension, diabetes mellitus, hypercholesterolemia, end-stage renal failure, smoking, drinking, a history of stroke, a history of heart disease, spontaneous echo contrast, left atrial appendage flow <46.9 cm/s, and left atrial dimension ≥42 mm.

Table 4. Sensitivity and specificity of parameters

	Sensitivity	Specificity	PPV	NPV
Parameters				
LAD ≥ 42 mm	0.60	0.70	0.19	0.94
LAAF < 46.9 cm/s	0.40	0.84	0.22	0.93
SEC	0.31	0.92	0.31	0.92
LAD and LAAF	0.31	0.95	0.42	0.93
LAD and SEC	0.17	0.96	0.35	0.91
All three factors	0.17	0.99	0.60	0.91

LAD, left atrial dimension in transthoracic echocardiography; LAAF, left atrial appendage flow in transesophageal echocardiography; SEC, spontaneous echo contrast in transesophageal echocardiography; PPV, positive predictive value; NPV, negative predictive value. All three factors: LAD, LAAF, and SEC.

Other findings or parameters were not significantly different between patients with and without PAF.

For parameters of TTE, LAD, left ventricular mass index, percent fractional shortening, and ejection fraction were evaluated. Only LAD was significantly higher in patients with PAF than in those without PAF ($p < 0.005$). The best cutoff point of LAD was 42 mm by receiver operating characteristic curve analysis.

Predictors of Echocardiographic Findings for PAF

Multivariate analyses were performed to exclude possible interaction among echocardiographic and clinical findings. SEC and LAD ≥ 42 mm were independently associated with PAF ($p < 0.05$, Table 3). An association of LAAF < 46.9 cm/s and PAF was marginal ($p = 0.09$, Table 3).

The sensitivity and specificity of three echocardiographic findings (SEC, LAAF < 46.9 cm/s, and LAD ≥ 42 mm) for predicting CPAF are shown in Table 4. The specificity of the LAD finding alone was not high (approx. 70%), but that of combination findings of SEC and/or LAAF with LAD increased to $> 90\%$. The sensitivity of LAD was 60%, while that of SEC, LAAF, or their combination was $< 40\%$.

Discussion

Previous studies have shown that some clinical parameters, such as age, frequent premature atrial contraction, mitral regurgitation, an increased left atrial diameter or volume, an increased left ventricular diameter, and a large cerebral lesion diameter, are associated with AF or PAF [12–17]. However, no single parameter may be useful for identifying patients at increased risk of CPAF in patients with ESUS because sensitivities and specificities of these parameters are not sufficiently high. With regard to echocardiographic findings, only a few studies have examined their association with CPAF as follows. Enlargement of the LAD [12], a low left atrial appendage ejection fraction [14, 15], and a low LAAF [14] have been shown to be predictors for PAF. In the present study, we also showed that enlargement of LAD by TTE and low LAAF by TEE were associated with PAF in patients with ESUS. We also showed that the presence of SEC was associated with CPAF. This is the first report to show that SEC can predict CPAF in patients with ESUS. However, SEC is reportedly associated with left atrial thrombus and embolism in patients with AF [18].

In our study, the specificity for detecting CPAF with an increased LAD by TTE was low (70%). However, a finding of LAD with that of SEC and/or LAAF dramatically increased the specificity. The specificity of three combined parameters (SEC, LAAF <46.9 cm/s, or LAD \geq 42 mm) was 99% in our study. Skaarup et al. [15] also showed that a combination of parameters (left atrial appendage ejection fraction <45%, minimal left atrial volume >23 mL, and age \geq 60 years) could be used to detect CPAF with a sensitivity of 95.0%. In patients with ESUS, detection of the embolic source is crucial for preventing recurrent stroke. Although a secondary prevention strategy of ESUS has not been established [19], we select anticoagulants when we strongly suspect the presence of PAF. The present findings of TEE in addition to TTE could contribute to selecting medication because the specificity became high after adding TEE findings.

The sensitivity of each single parameter of echocardiographic findings or that of their combination was not high in the present study. This finding is consistent with previous studies [14, 15]. The reason for this low sensitivity might be partly because CPAF could be overlooked. Better devices and/or methods, including an insertable cardiac monitor, are required for evaluating the sensitivity for detecting CPAF.

Our study has several limitations. First, this was a retrospective study based on medical records from a single center. However, the rate of lost to follow-up was low (3%). Second, our study has a possible sample selection bias. Although 76% of patients with ESUS underwent TEE, very old patients or those with a critical condition were excluded because of its invasiveness. Third, we did not assess the interrater reliability of echocardiography, although skilled ultrasonographers and neurologists, respectively, performed TTE and TEE. Fourth, CPAF might exist during the admission, although ECG monitoring or Holter ECG were performed in all patients. However, we could not completely exclude CPAF at the moment. Finally, an attempt to detect CPAF was not systematically performed. However, our hospital and affiliated clinics shared a consensus protocol for detecting CPAF. Therefore, CPAF might have been missed in some patients, and the detection rate of CPAF might have been underestimated.

Conclusion

The present study shows that findings of TEE in addition to those of TTE may be useful for identifying patients at increased risk of CPAF in cases of ESUS.

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Statement of Ethics

This retrospective study was approved by our institutional ethics review board, and informed consent for each patient was waived because of the retrospective nature of this study.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yuichiro Ohya and Masato Osaki designed the study and wrote the initial draft of the manuscript. Shuji Arakawa contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other authors contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the paper and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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