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A novel probe attached to the neck can accurately detect a large patent foramen ovale☆

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ABSTRACT

Purpose: We developed a novel probe (pastable soft ultrasound probe; PSUP) attached to the neck for right-to-left shunt (RLS) detection. The purpose of this study was to evaluate the diagnostic ability of the PSUP for RLS detection by comparison with transesophageal echocardiography (TEE).

Methods: The subjects were patients with ischemic strokes and transient ischemic attacks who underwent TEE. Based on TEE, patients with patent foramen ovale (PFO) were divided into two groups by the number of microbubbles (MBs): small PFO (1–29 MBs) and large PFO (≥30 MBs). Then, PSUP examination of one common carotid artery (CCA) was started using a procedure similar to TEE. RLS was diagnosed by PSUP when one or more microembolic signals were found in the CCA. The detection rate by size of PFO was compared between TEE and PSUP, and the diagnostic accuracy of PSUP was calculated.

Results: From May 2014 to July 2016, 84 patients (63 males, median age 63 years) were included; 41 (49%) were diagnosed with PFO by TEE, while PSUP detected PFO in 31 (37%). Using TEE findings as the reference, PSUP for PFO showed sensitivity of 68%, specificity of 93%, and accuracy of 81%. On TEE, 22 patients had large PFOs, and 19 patients had small PFOs. The PSUP could identify large PFOs in grade I and II of International Consensus Criteria more accurately than small ones (58 and 86% vs. 29 and 14%, $P = 0.003$).

Conclusions: The PSUP has considerable accuracy for diagnosing large PFOs. PSUP should play an important role in detecting large PFOs.

1. Introduction

Since right-to-left shunt (RLS) is a well-known cause of cryptogenic stroke [1–3], it is clinically important to identify RLS for secondary prevention of ischemic stroke. In order to identify patent foramen ovale (PFO), we commonly use transesophageal echocardiography (TEE) and/or transcranial Doppler (TCD). The diagnostic sensitivity of RLS by TCD is similar to that of TEE [4–6]. However, there are two problems with TCD: it cannot be performed in elderly patients with an insufficient temporal bone window [7]; and TEE is a slightly invasive examination for acute stroke patients.

We therefore developed a novel probe (pastable soft ultrasound probe; PSUP) that attaches easily to the neck at the carotid artery to identify RLS, because ultrasound can penetrate the soft tissue of the neck in most stroke patients. Thus, the goal of this study was to investigate the clinical usefulness of the PSUP for RLS diagnosis in comparison with TEE as the gold standard for RLS detection.

2. Methods

2.1. Subjects

The subjects were patients with acute ischemic stroke within 7 days after onset of symptoms or transient ischemic attack (TIA) who had undergone TEE in order to investigate the etiology of ischemic stroke and TIA. Because the purpose of this study was to evaluate the diagnostic power of a novel probe (PSUP) for PFO, patients with other RLS diseases, such as pulmonary arteriovenous fistula and atrial septal

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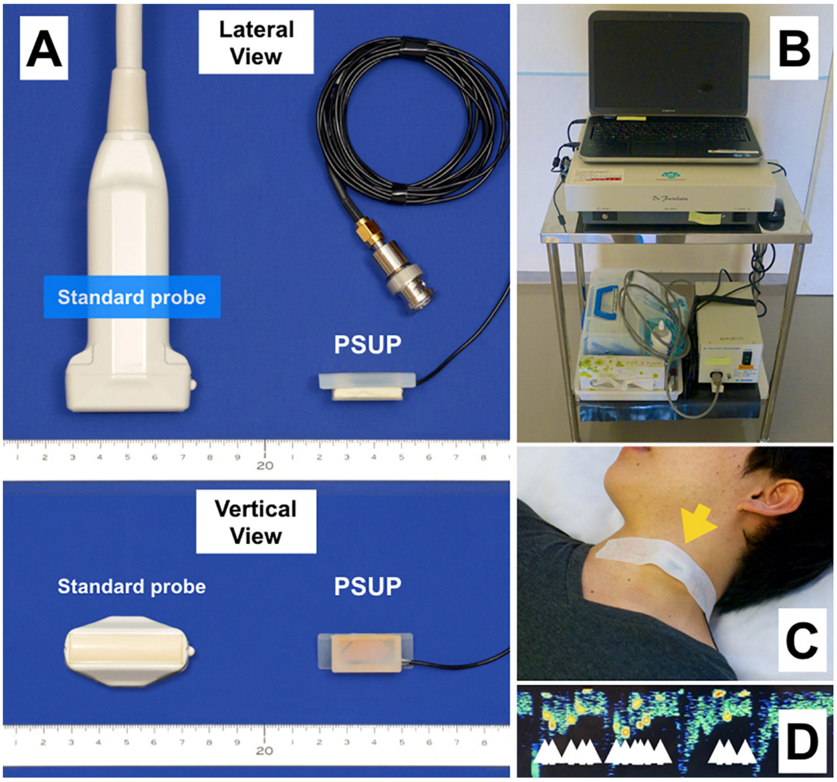

Fig. 1. Shape of PSUP (A) and ultrasound system appearance (B). PSUP attached to the neck (C) and cMES detected by PSUP (D). A, The PSUP has a thin and square shape modified for attachment to the neck. The PSUP is smaller than the standard linear probe for examination of the carotid artery. B, The ultrasound system including the PSUP is compact, as for TCD. C, The PSUP could be attached to the neck easily using surgical tape (arrow). D, On the sonogram of CCA, MES-induced contrast agents are detected by PSUP (arrows). Because the flow direction of CCA receded from the probe, the sonogram shows a downward wave.

defect, were excluded. The following clinical parameters were assessed in all patients: [1] age and sex; [2] stroke risk factors including hypertension, diabetes mellitus, dyslipidemia, and atrial fibrillation; and [3] ischemic stroke subtype determined according to Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria [8]. This study was performed in accordance with the guidelines of the Ethics Committee of Jikei University Hospital, and informed consent was obtained from each patient.

2.2. Characteristics of the novel probe and ultrasound system

We developed a novel probe (PSUP) and ultrasound system attached to the neck to detect microembolic signals (MESs) at the carotid artery (Fig. 1A, B). The PSUP is square and thin, modified for attachment to the neck, with a depth of 7 mm, width of 20 mm, and height of 4 mm (Fig. 1A). The probe transmits the ultrasound beam with a width of 15 degrees, and a soft silicone wedge was attached to the surface of the probe at an angle of 10 degrees to the skin. The properties of the PSUP are the same as those of TCD (center frequency 2.0 MHz, pulse repetition frequency 5000 Hz, and sample volume 7 mm). The ultrasound system includes the body core of the machine, the display screen, an insulating transformer, and the novel probe (HDK-MB001, Hashimoto Electronic Industry Co. Ltd., Matsusaka, Japan) (Fig. 1B).

2.3. TEE examination

TEE was performed using an EUB-7500 (HITACHI Healthcare, Tokyo, Japan) with a 5.0-MHz wideband omniplane probe. The patients received local pharyngeal anesthesia with lidocaine spray and were kept awake during the examination without premedication. After the probe was set at the level of the fossa ovalis, contrast agent (agitated 9 ml saline/1 ml air mixture) was injected into the right anterior cubital vein 5 s after the Valsalva maneuver was started using a three-way stopcock connected to two 10-ml syringes. After the right atrium was filled with contrast agent, the Valsalva maneuver was released. The procedure was also performed without the Valsalva maneuver. PFO was considered present if at least one microbubble (MB) of contrast agent was seen in the left atrium within three heartbeats. PFOs were classified according to the number of MBs as follows: small PFO (1–29 MBs) and large PFO (≥30 MBs) [9].

2.4. PSUP examination

The PSUP was fixed to the neck using surgical tape after the location and depth for sufficient monitoring of the unilateral common carotid artery (CCA) were identified (Fig. 1C). After preparation of the same contrast agent as for TEE examination, the contrast agent was injected immediately as a bolus into the right anterior cubital vein before the Valsalva maneuver. The Valsalva maneuver was started 5 s after contrast agent injection was begun and maintained for at least 5 s [10, 11]. A single test without the Valsalva maneuver and three tests with the Valsalva maneuver were performed. Using the PSUP, the presence of RLS was defined as the identification of one or more MESs in the CCA caused by the contrast agent (cMES) [12] (Fig. 1D). Moreover, a four-level categorization was using due to cMES appearance in the PSUP spectrum: negative; no occurrence of cMES, grade I; 1–10 cMES, grade II; > 10, but no curtain, and grade III; curtain (International Consensus Criteria; ICC) [11].

2.5. Analysis

PSUP examination was performed within one week of TEE evaluation. The sensitivity, specificity, and accuracy of detecting RLS by PSUP were calculated using TEE findings as the gold standard for PFO diagnosis. Fisher's exact test was used to compare the sensitivity of PSUP examination by size of PFO (small and large PFOs) in ICC categorizations. $P < 0.05$ was considered significant. Statistical tests were performed using PASW Statistics 18 for Windows (SPSS, Inc., Chicago, IL, USA).

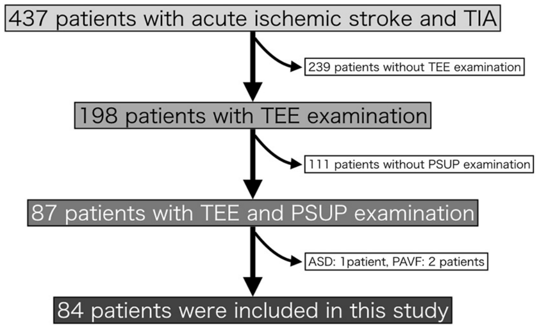

Fig. 2. The number of patients according to inclusion criteria. Eighty seven of 437 patients with acute ischemic stroke and TIA underwent TEE and PSUP. Of 198 patients who underwent TEE examination, informed consent was not obtained from 2 patients, and 109 patients were discharged immediately after TEE examination. Finally, 84 patients except 2 pulmonary arteriovenous fistulas (PAVFs) and an atrial septal defect (ASD) were included in this study.

3. Results

A total of 84 patients (63 males, median age 63 years) were evaluated from May 2014 to June 2016 (Fig. 2). Table 1 shows the subjects' baseline characteristics. PFO was detected by TEE in 41 patients (49%) (19 small PFOs and 22 large PFOs), whereas PSUP examination identified 31 patients with RLS (37%, ICC categorization: grade I; 24, grade II; 7, grade III; 0). Eight examinations had to be repeated because of PSUP failure or detachment with minor modification.

The results of RLS examination by PFO size are shown in Table 2. In the analysis of the presence or absence of PFO, PSUP examination showed 28 true positives, 3 false positives, 13 false negatives, and 40 true negatives (sensitivity, 68%; specificity, 93%; accuracy, 81%). For a large PFO on PSUP examination, there were 19 true positives, 12 false positives, 3 false negatives, and 50 true negatives (sensitivity, 86%; specificity, 81%; accuracy, 82%).

As shown in Fig. 3, the prevalence of large PFOs by PSUP examination showed 14 of 24 (58%) in grade I and 6 of 7 (86%) in grade II, but small PFOs showed only 7 of 24 (29%) in grade I and 1 of 7 (14%) in grade II. The prevalence of large PFO increased along with ICC categorization. The sensitivity using PSUP was significantly higher for large than for small PFOs in grade I and II ($P = 0.003$).

Table 1
Subjects' characteristics.

	$N = 84$
Male, n (%)	63 (75.0)
Age, years, median (25–75%tile)	63 (49–72)
Risk factors, n (%)	
Hypertension	51 (60.7)
Dyslipidemia	44 (52.4)
Diabetes	23 (27.4)
Smoking	49 (58.3)
Atrial fibrillation	8 (9.5)
Subtype of cerebral infarction, n (%)	
Large-artery atherosclerosis	3 (3.6)
Cardioembolism	14 (16.7)
Small-vessel occlusion	7 (8.3)
Other and undetermined etiology	46 (54.8)
Transient ischemic attack, n (%)	14 (16.7)
Right-to-left shunt detected by TEE, n (%)	
All PFO	41 (48.8)
Small PFO	19 (22.6)
Large PFO	22 (26.2)
Contrast MES appearance by PSUP, n (%)	
Negative	53 (63.1)
Grade I	24 (28.6)
Grade II	7 (8.3)
Grade III	0 (0.0)

TEE, transesophageal echocardiography; PFO, patent foramen ovale; MES; microembolic signals, PSUP; pastable soft ultrasound probe.

Table 2
RLS examination according to the size of PFO.

		TEE		
		PFO (−)	Small PFO	Large PFO
PSUP	RLS (−)	40	10	3
	RLS (+)	3	9	19

The presence of PFO: Sensitivity, 68%; Specificity, 93%; Accuracy, 81%.
The presence of large PFO: Sensitivity, 86%; Specificity, 81%; Accuracy, 82%.
RLS, right-to-left shunt; PFO, patent foramen ovale; PSUP, paste-able soft ultrasound probe; TEE, transesophageal echocardiography.

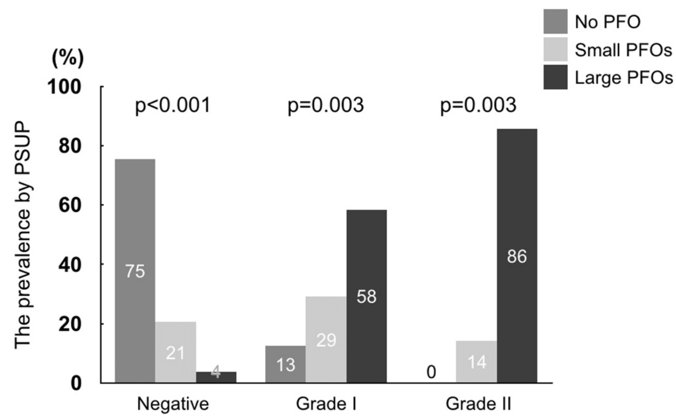

Fig. 3. The prevalence of PFO using PSUP among ICC categorizations. Large PFOs could be detected with greater sensitivity than small PFOs by PSUP in grade I (58% vs. 29%, $p = 0.003$) and grade II (86% vs. 14%, $p = 0.003$).

4. Discussion

The present study had two major findings: the diagnostic accuracy of the PSUP for PFO was sufficiently high compared with TEE; and the PSUP more accurately detected large than small PFOs.

The diagnostic accuracy for PFO was compared between PSUP and TEE. The present approach is partially in line with previous studies using conventional duplex carotid ultrasonography (DCU) [13] and TCD [14–17] in cases with an insufficient temporal bone window. In the present study, the MES detection rate was significantly higher by PSUP than by DCU. The reason for this is that the 2.0-MHz transducer of PSUP is adequate for detecting MESs in comparison with DCU using a transducer frequency > 7.0-MHz [18]. Second, PSUP attachment to the neck to examine the carotid artery is stable and easy. It is difficult to handle the TCD probe from a submandibular window for a long time, because the device for attaching the TCD probe has little stability [13, 16]. Thus, when we would like to diagnose PFO by less invasive equipment, the PSUP has a major advantage, especially in cases without a patent temporal bone window, such as Asian or elderly patients.

In the present study, PSUP examination could identify a large PFO with a high sensitivity. This is in agreement with a previous report by Kobayashi et al. [19] The reason why it is important to detect large PFOs is that PFO size is strongly associated with the neurological deficits that occur with stroke onset and stroke recurrence [20, 21]. For cryptogenic stroke with PFO, transcatheter PFO closure may be effective for preventing recurrent stroke, especially in patients with a large PFO [22, 23] [24–26]. As shown these latest PFO closure trials, cryptogenic stroke was defined due to exclude other identifiable mechanisms of stroke by means of several imaging including TEE. Although TEE is the gold standard for PFO diagnosis and evaluation of aortic arch's plaque, it is occasionally difficult to conduct TEE for acute stroke patients because of their dysphagia and consciousness disturbances. Thus, the relatively non-invasive, easy, and low skilled PSUP examination should play an important role in screening for large PFOs and selecting therapeutic options.

This study had several limitations. First, the subjects were patients who had been transferred to another facility prior to obtaining informed consent. Then, in order to avoid artifacts caused by noise, sleep, and cough on the Doppler waveform of PSUP, attaching the probe onto the neck required some skill. Because these noisy signals during swallowing a TEE probe could disturb steady monitoring by the PSUP, simultaneous PSUP and TEE examinations were not possible.

In conclusion, PSUP showed substantial specificity and accuracy for the diagnosis of PFO; in particular, large PFOs could be detected with high accuracy. PSUP examination provides a novel, non-invasive method to easily evaluate the risk of cryptogenic stroke, especially for patients with an inadequate temporal bone window for TCD.

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Author contributions

Ayumi Arai, acquisition of data as neurosonographer.
Takeo Sato, acquisition of data.
Teppei Komatsu, acquisition of data.
Kenichi Sakuta, acquisition of data.
Kenichiro Sakai, acquisition of data.
Yuka Terasawa, acquisition of data, study supervision.
Jun Kubota, Development of the device, study concept and design.
Yasuyuki Iguchi, analysis and interpretation of data, critical revision of manuscript.

Author disclosures

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