Circulation Journal
Circ J 2024; 88: 1398–1405
doi:10.1253/circj.CJ-24-0313

ORIGINAL ARTICLE
ACHD

# Morphological Features of Patent Foramen Ovale Compared Between Older and Young Patients With Cryptogenic Ischemic Stroke

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***Background:*** The morphology of a patent foramen ovale (PFO) with a high-risk for cryptogenic ischemic stroke (CS) is an important factor in the selection of patients for transcatheter closure, but the morphological features of PFO in older patients with a history of CS are less known because the most data are obtained from younger patients.

***Methods and Results:*** The study included 169 patients who had a history of CS and PFO. The prevalence of high-risk morphologies of PFO assessed by transesophageal echocardiography was compared between patients aged ≥60 years and patients aged <60 years. We also assessed the presence of septal malalignment of PFO on the aortic wall. The probability of CS due to PFO was evaluated using the PFO-Associated Stroke Causal Likelihood classification system. Patients aged ≥60 years had a significantly higher prevalence of atrial septal aneurysm than patients aged <60 years. The prevalence of large right-to-left shunt, long-tunnel of PFO, or Eustachian valve or Chiari's network was similar between patients aged ≥60 years and <60 years. Septal malalignment was observed more frequently in patients aged ≥60 years than in those <60 years old. Nearly 90% of patients aged ≥60 years were classified as 'possible' in the PFO-Associated Stroke Causal Likelihood classification system.

***Conclusions:*** High-risk morphologies of PFO are common in older patients with a history of CS, as well as in younger patients.

**Key Words:** Cryptogenic ischemic stroke; Older patients; Patent foramen ovale

Patent foramen ovale (PFO) is widely recognized as a risk for cryptogenic ischemic stroke (CS),[1,2] and transcatheter closure is reportedly effective in reducing the incidence of recurrent stroke compared with medical therapy.[3–6] Identifying patients with CS due to PFO is conventionally recommended to comply with the RoPE score,[7] but this score is not commonly used in older patients,[8] who are considered to have a lower prevalence of CS due to PFO.[9–11] Therefore, most previous studies investigating the efficacy of transcatheter closure have only included patients <60 years.[3–5] However, the morphology of PFO can be affected by acquired factors,[12] so CS due to PFO can occur in patients aged ≥60 years and thus it is important to understand the clinical features of CS due to PFO in this age group, for whom there is limited clinical data.

Several specific morphologies of PFO have been reported as presenting a high risk for CS,[13–15] but only 1 randomized control trial, the DEFENSE-PFO trial, which targeted patients with high-risk PFO morphologies, included not only patients aged <60 years but also those ≥60 years.[6] A subgroup analysis of DEFENSE-PFO suggested that transcatheter PFO closure may be effective to reduce the recurrence of stroke in older patients (≥60 years).[16] Indeed, in the clinical setting, almost one-third of transcatheter PFO closures were performed in patients >60 years in the Amplatzer™ PFO Occluder Japan Post-Marketing Surveillance study.[17] Therefore, preoperative evaluation of the morphology of the PFO may be important when considering the indication of transcatheter closure, especially in older patients with a history of CS. Therefore, because the morphological features of PFO in older patients with a history of CS are comparatively unknown our aim in the present study was to rectify this deficiency in the data.

Received April 22, 2024; revised manuscript received May 10, 2024; accepted May 13, 2024; J-STAGE Advance Publication released online June 11, 2024 Time for primary review: 9 days

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ISSN-1346-9843

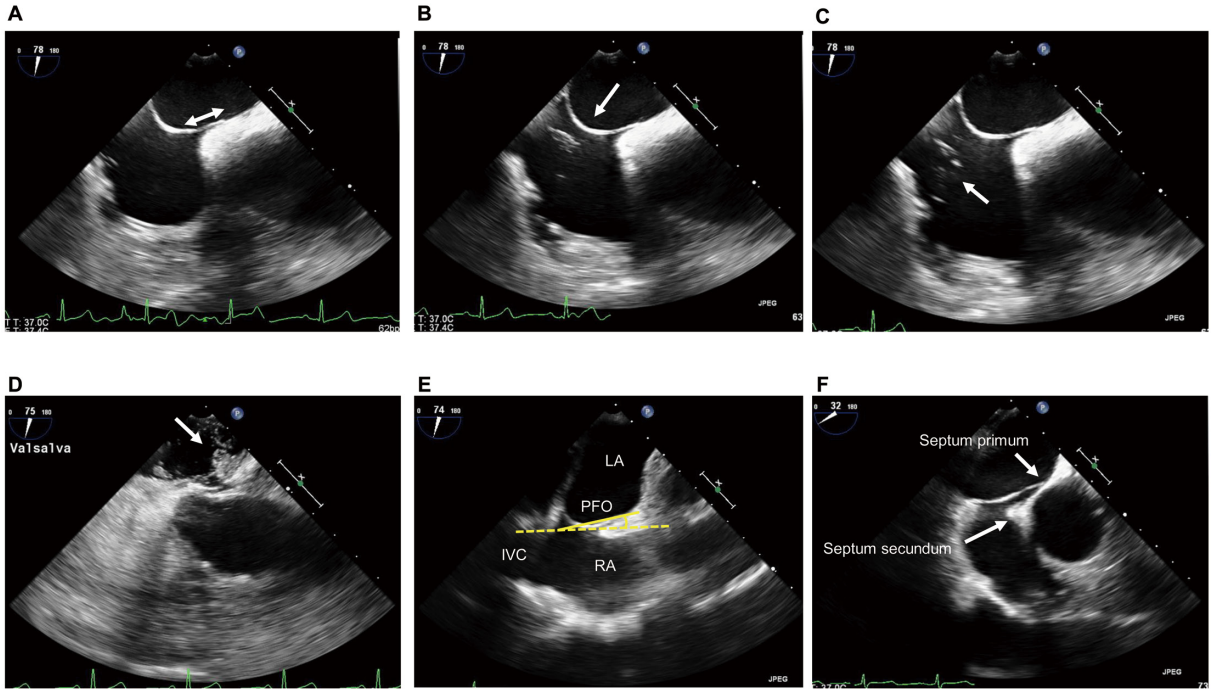


**Figure 1.** Representative high-risk morphologies of PFO on TEE. (**A**) Double-headed arrow shows a long-tunnel of PFO, defined as a maximum length of the overlap between the septum primum and septum secundum ≥10 mm. (**B**) Arrow shows a widely mobile interatrial septum. ASA was defined as septal excursion ≥10 mm from the midline into the right or left atrium or a total excursion of ≥15 mm between the right and left atria. A hypermobile interatrial septum was defined as a mobile and floppy septum with ≥5 mm of septal excursion. (**C**) Arrow shows a prominent Eustachian valve in the right atrium, defined as ≥10 mm protrusion. (**D**) Arrow shows microbubbles occurring with agitated saline contrast, and a large RL shunt was defined as ≥20 microbubbles in the left atrium counted in a single frame during the Valsalva maneuver. (**E**) Yellow lines show the angle of the PFO (solid line) from the IVC (dotted line), and a low-angle PFO was defined as angle ≤10°. (**F**) Arrows show the septal malalignment. The septum primum was malaligned toward the left atrial side and separated from the septum secundum on the aortic wall. ASA, atrial septal aneurysm; IVC, inferior vena cava; LA, left atrium; PFO, patent foramen ovale; RA, right atrium; RL, right-to-left.

## Methods

### Study Population

A total of 169 consecutive patients with a history of CS who underwent transesophageal echocardiography (TEE) and were detected as having a PFO at Okayama University Hospital between June 2008 and January 2022 comprised the study population. CS was defined as an imaging-confirmed stroke with unknown source despite thorough diagnostic assessment.[7] Stroke was defined as a documented, symptomatic focal neurological deficit, accompanied by findings on computed tomography (CT) scan or magnetic resonance imaging (MRI). In our clinical practice, diffusion-weighted MRI is prioritized as the imaging modality for diagnosis of stroke, and if MRI cannot be performed due to the presence of implanted medical devices, CT scan, including contrast three-dimensional imaging, is considered. A transient ischemic attack without cerebral ischemic imaging findings was not included as stroke in this study. Cortical infarcts are typically considered as a finding of CS, and small vessel lesions are regarded as low probability of CS.[8] CS was diagnosed by neurologists after exclusion of other alternative causes of stroke, including lacunar, large artery atherosclerosis or cardiogenic embolism after neurological and cardiac imaging tests such as brain CT scan, MRI findings, ECG and echocardiography. In particular, exclusion of paroxysmal atrial fibrillation was carefully conducted in all patients using Holter monitoring or implantable cardiac monitor. Cardiac monitoring was usually continued for >1 week, and if it was not available, 24-h Holter testing was repeatedly evaluated.

This study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Okayama University Hospital. Written informed consent for the examinations and participation in the study was given by all patients.

### Transthoracic Echocardiography

All patients underwent TTE before or at the same time of TEE, and the data were collected from their hospital records. TTE was performed by experienced technicians using a high-quality commercial ultrasound system (iE33, Philips Medical Systems, Andover, MA, USA; Atrida, Toshiba Medical Systems, Tokyo, Japan). The TTE findings were confirmed by 3 experienced investigators (M.N., R.N. and M.T.) who were unaware of the clinical data. TTE parameters were measured according to the current guidelines from the American Society of Echocardiography.[18–21] We measured the left ventricular end-diastolic diameter, left ventricular end-systolic diameter and maxi-

**Table 1. Baseline Clinical Characteristics**

| Variables | All patients (n=169) | ≥60 years (n=66) | <60 years (n=103) | P value |
|---|---|---|---|---|
| Age, years | 53±15 | 68±6 | 43±10 | <0.001 |
| Female | 66 (39.1) | 25 (37.9) | 41 (39.8) | 0.929 |
| Hypertension | 52 (31.4) | 33 (50.0) | 19 (18.4) | <0.001 |
| Dyslipidemia | 46 (27.2) | 26 (39.4) | 20 (19.4) | 0.008 |
| Diabetes mellitus | 14 (8.3) | 11 (16.7) | 3 (2.9) | 0.004 |
| Smoking | 34 (20.1) | 15 (22.7) | 19 (18.4) | 0.631 |
| Prior deep venous thrombosis | 34 (20.1) | 16 (24.2) | 18 (17.5) | 0.382 |
| Prior transient ischemic attack | 10 (5.9) | 4 (6.1) | 6 (5.8) | 1.000 |

Data are presented as the number (%) or mean±standard deviation.

**Table 2. Transthoracic Echocardiographic Findings of Patients Divided by Age 60 Years**

| Variables | ≥60 years (n=66) | <60 years (n=103) | P value |
|---|---|---|---|
| Left atrial volume index, mL/m$^2$ | 33.0 (29.0–38.0) | 30.0 (25.0–33.0) | <0.001 |
| Left ventricular end-diastolic diameter, mm | 44.6±4.3 | 47.2±4.0 | <0.001 |
| Left ventricular end-systolic diameter, mm | 28.3±3.3 | 30.1±3.5 | 0.001 |
| Left ventricular mass index, g/m$^2$ | 79.4±17.7 | 80.1±16.6 | 0.797 |
| Left ventricular ejection fraction, % | 65.5±5.0 | 65.4±5.4 | 0.912 |
| e′, cm/s | 6.0±1.8 | 9.1±2.6 | <0.001 |
| E/e′ | 9.8±3.3 | 7.7±1.9 | <0.001 |
| Tricuspid regurgitation pressure gradient, mmHg | 19.9±5.6 | 18.2±4.8 | 0.036 |
| Maximum inferior vena cava, mm | 11.5±3.9 | 11.4±3.8 | 0.852 |

Data are presented as the number (%) or mean±standard deviation.

mum diameter of the inferior vena cava using conventional methods. The left ventricular mass index was calculated as: left ventricular mass/body surface area. The left ventricular mass was calculated as: $0.8\times\{1.04\times[(\text{left ventricular end-diastolic diameter}+\text{intraventricular septum diameter}+\text{posterior wall diameter})^3-(\text{left ventricular end-diastolic diameter})^3]\}+0.6$.[22] Left ventricular ejection fraction and left atrial volume were measured using the biplane modified Simpson's method, and the left atrial volume index was indexed to the body surface area. The peak early diastolic velocities (E) of the left ventricular inflow and early diastolic myocardial velocities (e′) were measured, and the ratio of E and e′ (E/e′) was calculated. The tricuspid regurgitation pressure gradient was measured using the peak velocity of tricuspid regurgitation.

## PFO Morphologies

Under light sedation, the morphology of each patient's PFO was evaluated by TEE (iE33 with an X7-2t probe, Philips Medical Systems) performed by experienced cardiovascular physicians. These TEE findings were also confirmed by the 3 experienced investigators (M.N., R.N. and M.T.) who were unaware of the clinical data. We investigated the presence of long-tunnel of PFO, atrial septal aneurysm (ASA), hypermobile interatrial septum, prominent Eustachian valve or Chiari's network, a large right-to-left (RL) shunt during the Valsalva maneuver and a low-angle PFO.[5,13–15,23] **Figure 1** shows representative cases of all of these morphologies. Long-tunnel of PFO was defined as a maximum length of the overlap between the septum primum and septum secundum ≥10 mm (**Figure 1A**). Septal excursion was evaluated from the short-axis view (around 45°) to the bicaval view (around 90°) at the mid-esophageal view. ASA was defined as septal excursion ≥10 mm from the midline into the right or left atrium or a total excursion ≥15 mm between the right and left atria. Hypermobile interatrial septum was defined as a mobile and floppy septum with ≥5 mm of septal excursion throughout the heart beats (**Figure 1B**). Prominent Eustachian valve was defined as ≥10 mm protrusion within the right atrium (**Figure 1C**). A large RL shunt was defined as ≥20 microbubbles appearing in the left atrium counted in a single frame during the Valsalva maneuver using agitated saline contrast (**Figure 1D**). Low-angle PFO was defined as the angle of the PFO from the inferior vena cava ≤10° (**Figure 1E**).[13] In addition, we investigated the presence of septal malalignment, in which the septum primum is malaligned toward the left atrial side and separated from the septum secundum on the aortic wall (**Figure 1F**). Although this feature is reported as an important risk factor of procedural complication in transcatheter atrial septal defect closure, the clinical features of septal malalignment in patients with PFO have not been evaluated.[24]

Based on previous studies, a high-risk morphology satisfied 3 criteria. Criterion 1 was the presence of either ASA or a large RL shunt.[3,4,6,25–28] Criterion 2 was the presence of both ASA and a large RL shunt.[27] Criterion 3 was the presence of ≥2 factors among long-tunnel of PFO, hypermobile interatrial septum, Eustachian valve or Chiari's network, large RL shunt during Valsalva maneuver and low-angle PFO.[13]

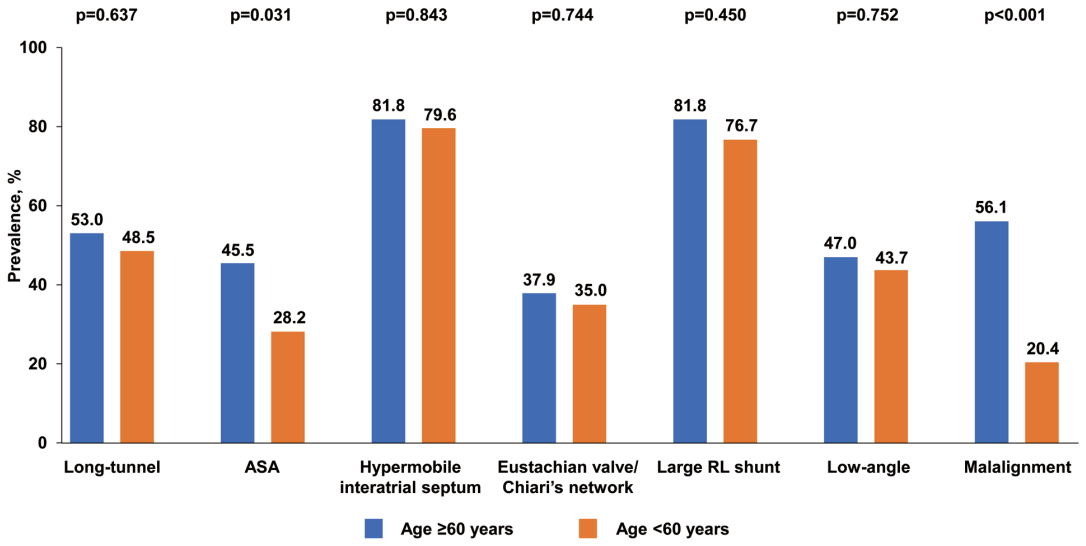


**Figure 2.** Prevalence of PFO morphologies. ASA, atrial septal aneurysm; PFO, patent foramen ovale; RL, right-to-left.

### Scoring for the Probability of CS Due to PFO

The probability of CS due to PFO was calculated for all patients using the RoPE score,[8] which is indexed by the absence of hypertension, diabetes mellitus, history of prior stroke or transient ischemic attack and smoking, the presence of a cortical infarct on imaging and age divided as follows: 18–29 years, 5 points; 30–39 years, 4 points; 40–49 years, 3 points; 50–59 years, 2 points; 60–69 years, 1 point; and ≥70 years, 0 points. Factors other than age are calculated as 1 point, respectively.

The PFO-Associated Stroke Causal Likelihood (PASCAL) classification system, which reflects both the RoPE score and the morphology of PFO, was also evaluated[26] according to (a) RoPE score <7 points or ≥7 points and (b) presence of ASA or a large RL shunt. In patients with RoPE score <7 points, those without the presence of ASA or a large RL shunt were classified as 'unlikely', while those with the presence of ASA or a large RL shunt were classified as 'possible'. In patients with RoPE score ≥7 points, those without the presence of ASA or a large RL shunt were classified as 'possible', while those with the presence of ASA or a large RL shunt were classified as 'probable'.

### Statistical Analysis

Categorical variables are presented as numbers (%) and were compared using the $\chi^2$ test or Fisher's exact test, as appropriate. Continuous variables that were normally distributed are presented as mean±standard deviation and were compared using Student's t-test. Continuous variables that were not normally distributed are presented as medians with interquartile ranges and were compared using the Mann-Whitney U test. To compare clinical findings, we divided patients by age 60 years. Statistical significance was set at P<0.05. Analyses were performed with SPSS statistical software (version 25; IBM Corp., Armonk, NY, USA) and the R statistical package (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Patients' Characteristics (Table 1)

The mean age of the 169 patients included in this study was 53±15 years, and 66 (39.1%) were male; 103 patients (60.9%) were aged <60 years and 66 (39.1%) were ≥60 years. The mean age of the patients ≥60 years was 68±6 years and 43±10 years in the patients < 60 years (P<0.001). The prevalence of hypertension, dyslipidemia and diabetes mellitus were significantly higher in patients aged ≥60 years than in patients <60 years (P<0.05, respectively). There were no differences in the sexes or smoking history between the 2 age groups.

Among the 169 patients, 149 (88.2%) underwent transcatheter PFO closure: 53 patients ≥60 years (80.3%) and 96 patients <60 years (93.2%).

### TTE Findings (Table 2)

The median left atrial volume index was significantly larger in patients ≥60 years than in patients <60 years (33.0 [29.0–38.0] mL/m$^2$ vs. 30.0 [25.0–33.0] mL/m$^2$, P<0.001). Left ventricular end-diastolic diameter, left ventricular end-systolic diameter and e′ were significantly lower in patients ≥60 years, while E/e′ and tricuspid regurgitation pressure gradient were significantly higher (P<0.05, respectively).

### PFO Morphologies

**Figure 2** shows the prevalence of the morphologies of PFO. Long-tunnel of PFO, Eustachian valve or Chiari's network, large RL shunt and low-angle of PFO were similarly prevalent in both age groups. The prevalence of ASA was significantly higher in patients ≥60 years than in patients <60 years (45.5% vs. 28.2%, P=0.031). Septal malalignment was also significantly more prevalent in patients ≥60 years (56.1% vs. 20.4%, P<0.001). **Figure 3** shows the prevalence of high-risk morphology of PFO for each criterion. The prevalence of criteria 1 and 3 was similar in both age groups, but the prevalence of high-risk PFO in criterion 2

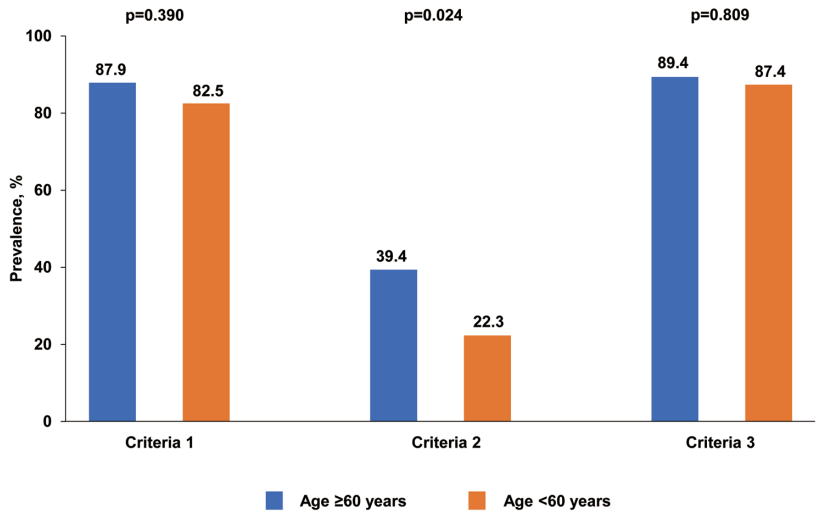


**Figure 3.** Prevalence of high-risk PFO for each criterion. PFO, patent foramen ovale.

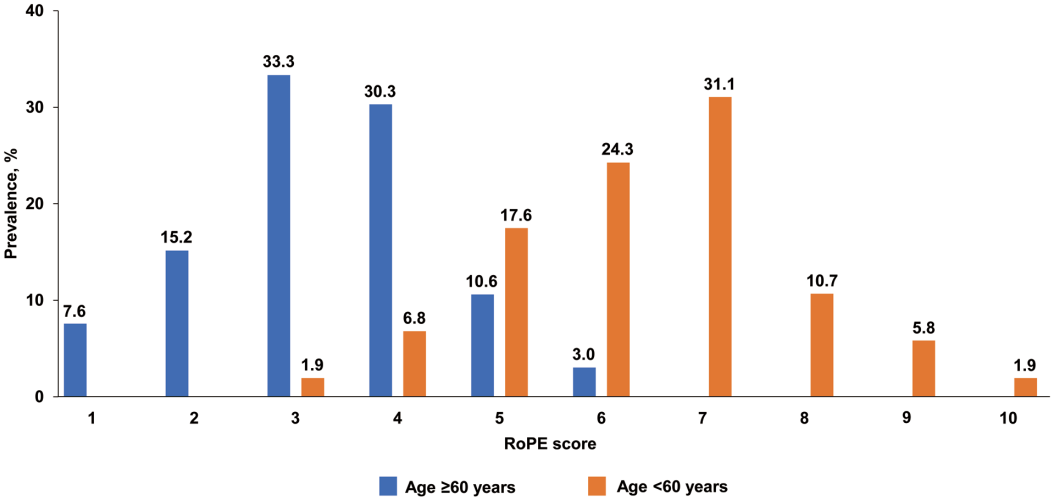


**Figure 4.** Distribution for prevalence of the RoPE score.

was significantly higher in patients ≥60 years than in patients <60 years (39.4% vs. 22.3%, P=0.024).

Because only ASA was significantly different between groups, further analyses were performed to evaluate the differences in the TTE findings according to the presence of ASA. Age was significantly higher in patients with ASA than in patients without ASA (58±13 vs. 51±15 years, P=0.002). Although e′ was significantly lower in patients with ASA than in patients without ASA (7.1±2.6 vs. 8.3±2.7 cm/s, P=0.011), there was no significant different between patients with and without ASA in left atrial volume index (30.0 [26.5–34.5] vs. 30.0 [26.0–34.8] mL/m$^2$, P=0.646), E/e′ (9.0±2.7 vs 8.2±2.6, P=0.106) and tricuspid regurgitation pressure gradient (19.2±5.0 vs. 18.6±5.3 mmHg, P=0.533).

### Scoring for the Probability of CS Due to PFO

The RoPE score was median 3 (3–4) points in patients ≥60 years and median 6 (5–7) points in patients <60 years. Among the patients ≥60 years, none had a RoPE score ≥7 points, and a PASCAL classification of 'unlikely' and 'possible' was given to 8 (12.1%) and 58 patients (87.9%), respectively. Among the patients <60 years, 51 (49.5%) had a RoPE score ≥7 points, and a PASCAL classification of 'unlikely', 'possible' and 'probable' was given to 10 (9.7%), 50 (48.5%) and 43 patients (41.7%), respectively. **Figure 4** and **Figure 5** show the distribution of the prevalence of the RoPE score and PASCAL classification in each group.

## Discussion

In the present study we investigated the morphological

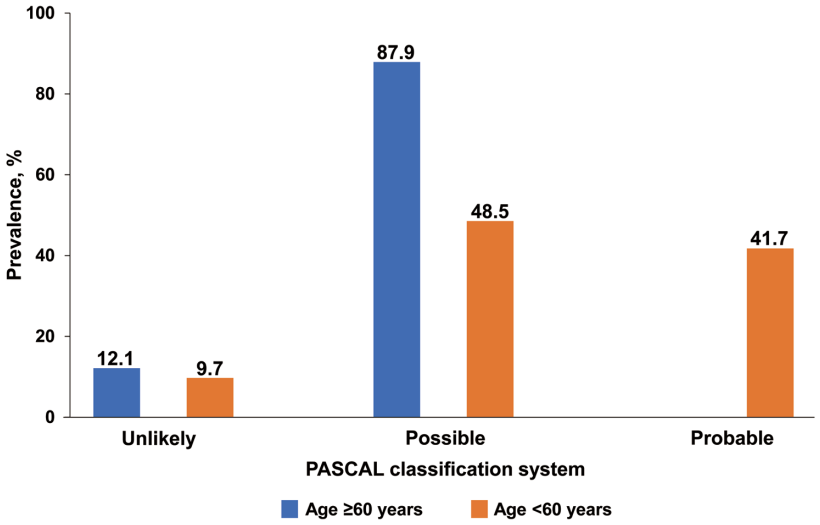


**Figure 5.** Distribution of the prevalence of the PASCAL classification system. PASCAL, PFO-Associated Stroke Causal Likelihood.

features of PFO in patients with a history of CS, including older patients aged ≥60 years. A high-risk morphology of PFO was frequently observed in patients ≥60 years, as well as in patients <60 years, although the RoPE score was significantly lower in patients ≥60 years. To our knowledge, this is the first study to evaluate the morphological features of PFO in older patients with a history of CS in comparison with younger patients.

### CS Due to PFO in Patients Aged ≥60 Years

The provability of CS due to PFO is assumed to be infrequent among older patients because other risk factors of stroke such as atherosclerosis and atrial fibrillation are increased in this patient cohort.[9–11] Therefore, most of the randomized control trials that have evaluated the efficiency of transcatheter closure have only included patients <60 years, and the clinical features of CS due to PFO has been scarcely investigated in patients ≥60 years.[3–5] However, PFO causes CS not only in patients <60 years but also in patients ≥60 years, because its morphology can be influenced by acquired factors.[12] In addition, the prevalence of deep venous thrombosis, which is an important cause of CS through a PFO, increases in the older population.[29] Indeed, the DEFENSE-PFO trial reported the efficacy of transcatheter PFO closure in patients ≥60 years, as well as those aged <60 years.[6,16] That result indicates that PFO may cause CS even in patient ≥60 years. According to the real-world data from the Amplatzer™ PFO Occluder Japan Post-Marketing Surveillance study, 29.8% of patients who underwent transcatheter PFO closure were aged >60 years, based on their clinical background and the morphological findings of PFO on TEE.[17] Therefore, it seems reasonable to investigate the presence and morphology of PFO in patients ≥60 years who have a history of CS.

### Morphological Features of PFO According to Patients' Age

Although PFO is observed in approximately 25% of individuals in the general population, not all PFOs cause paradoxical embolism.[30] As such, recent studies have reported the morphological features of PFO associated with an increased risk of paradoxical embolism.[13,26–28] In the present study, high-risk morphologies of PFO were frequently observed in both the older and younger patients. Although the differences in older patients with and without a history of CS were not revealed, a high-risk PFO morphology might be an important risk factor for stroke among not only in younger patients but also older patients.

In particular, the prevalence of criterion 2 for a high-risk morphology of PFO was higher in older patients, which seemed to be attributed to a difference in the prevalence of ASA. ASA is the clinically important morphology because it is associated with both the risk of CS and of residual shunt after transcatheter PFO closure.[31] Therefore, preoperative evaluation for ASA may be especially important for older patients with a history of CS. Previous reports have also shown that ASA is more frequently observed among relatively older patients rather than young patients.[32,33] The pathological mechanisms of these differences in the prevalence of ASA are unclear, but acquired factors may potentially influence it and not only the congenital factors.[34] Acquired factors such as increased pressure gradient between interatrial septum or cardiac remodeling may induce a vulnerable atrial septum, whether congenital or acquired, to develop ASA. However, only age and e′ were significantly different between patients with and without ASA in this study. A lower e′ in patients with ASA indicates left ventricular diastolic dysfunction, which may cause an elevated left-sided filling pressure and thus a pressure imbalance across the intra-atrial septum. However, other parameters related to left ventricular diastolic dysfunction or elevated left ventricular filling pressure such as E/e′ and tricuspid regurgitation pressure gradient were not significantly different between presence or absence of ASA in this study. Therefore, the main reason for the higher prevalence of ASA in older patients was not identified in this study and future large longitudinal cohort studies are needed to elucidate the pathological mechanisms of age-related changes in PFO morphology.

The present study showed that older patients had a high rate of septal malalignment of the PFO on the aortic wall, the clinical implication of which has not been previously investigated. This result suggests that the prevalence of

septal malalignment also increases with age and acquired factors. Indeed, older patients have many acquired structural changes, such as cardiac remodeling and changes in the relationship between the atrial septum and the ascending aorta due to dilation, horizontal angle or tortuosity of the ascending aorta. However, these mechanisms of septal malalignment could not be identified in this study, because the focus was on evaluation of the morphology of PFO by TEE and the study protocol did not include sufficiently detailed evaluation of aortic angle or tortuosity on an appropriate modality such as three-dimensional CT. Further analyses for pathological mechanisms of septal malalignment in PFO are required.

### Scoring for the Probability of CS Due to PFO

The RoPE score is widely recommended for evaluating the probability of CS due to PFO,[7] and a score ≥7 points is interpreted as a high probability of CS due to PFO.[8,25,26] However, patients aged ≥60 years will never have a RoPE score ≥7 points, because of the calculation parameters. As has been already noted, CS due to PFO can occur in older patients, and in a clinical setting older patients were diagnosed as CS due to PFO and underwent transcatheter PFO closure.[17] From this perspective, some studies suggest that morphological assessment should be added to the RoPE score.[25,26] Indeed, the PASCAL classification system, which is calculated using the RoPE score and the presence of high-risk morphologies of PFO, has come into recent usage and has a greater precision than evaluation by RoPE score alone in identifying patient populations with a higher probability of a relationship between CS and PFO and with greater benefit of PFO closure.[26] In this study, nearly 90% of older patients were classified as 'possible' using the PASCAL classification system. A previous study reported that patients who were classified as 'possible' had a favorable reduction in recurrent stroke after transcatheter PFO closure, as well as patients who were classified as 'probable'.[26] On the other hand, only one-eighth of the older patients in that study were classified as 'unlikely', which is reported as having a low probability of a relationship between CS and PFO and the less benefit of transcatheter PFO closure.[26] Therefore, probability assessment using the PASCAL classification system rather than the RoPE score alone may be reasonable for older patients.

### Study Limitations

First, this was a single-center, retrospective study with a relatively small sample size; a multicenter prospective study with a larger sample size is required to confirm our findings. Second, only patients who underwent TEE were enrolled. Some older patients might not have been included in this study because they could not undergo TEE because of their frailty or decreased ability to perform activities of daily living after a stroke. In addition, some older patients who were not considered to be candidates for transcatheter PFO closure due to their age may not have undergone TEE. This may constitute a selection bias. Third, evaluation of the grade of RL shunt might depend on the degree of the Valsalva maneuver. Some patients might not be capable of performing an adequate Valsalva maneuver, due to neurological disorders after stroke. In addition, patients were lightly sedated during the TEE procedure, so the grade of RL shunt might have been underestimated. However, all patients underwent the procedures of TEE and Valsalva assessment uniformly at a single institution. Finally, the time course of changes in the morphology of PFO was not obtained. Because this study was retrospective and there was not repeated TEE observation of the same patients, we could not determine whether the high-risk morphologies of PFO seen in the older patients would have been observed when they were younger or had developed through the influence of acquired factors.

## Conclusions

High-risk morphologies of PFO were observed in older patients with a history of CS, as well as in younger patients. In patients with a history of CS, the diagnosis and evaluation of PFO morphologies should be performed, even in older patients without a RoPE score.

### Acknowledgments

None.

### Disclosures

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### IRB Information

This investigation was approved by the Institutional Review Board of Okayama University Graduate School of Medicine (1812-009).

### Data Availability

The deidentified participant data will be shared on request. Please contact the corresponding author directly to request data sharing. Data on patient and procedural characteristics will be shared. The study protocol will also be available. The data will be available for 2 years after the publication of the study and will be provided as PDF files sent by email.

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