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Age-Related Variations in Patterns of Patent Foramen Ovale-Stroke versus Other Cryptogenic Stroke

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Cryptogenic stroke · Patent foramen ovale · Neuroimaging

Abstract
Introduction: Patent foramen ovale (PFO)-stroke, a form of cryptogenic stroke, has certain identifying clinical and imaging features. However, data describing this stroke type remain inconsistent. This study examined the potential variations in PFO-stroke features, depending on age. ***Methods:*** From a hospital registry, cryptogenic stroke patients were retrospectively selected, and PFO-strokes were identified by the presence of >10 microembolic signals on transcranial Doppler saline agitation test. Cryptogenic strokes were grouped according to age (<70 as young, ≥70 as elderly). Clinical and imaging variables of PFO-strokes and non-PFO-strokes were compared, with and without age considered. ***Results:*** Of the 462 cryptogenic patients, 30.5% (141/462) were PFO-strokes, while majority (321/462) had no PFO. When cryptogenic strokes were analyzed by age, the significant difference was noted in the lesion number, pattern, and side. A single (72.8 vs. 57.9%, $p = 0.020$) and a small single lesion (51.1 vs. 35.5%, $p = 0.039$) were frequently seen in the younger PFO-strokes than the non-PFO counterpart, while mixed territory lesions identified the elderly PFO-strokes (30.6 vs. 8.9%, $p = 0.001$). A multivariate logistic regression analysis of PFO-strokes further showed that age was independently associated with lesion side (OR 1.12 [1.05–1.20], $p < 0.001$) and lesion number (OR 1.06 [1.02–1.10], $p = 0.005$). ***Conclusions:*** Incorporating age-specific imaging criteria in the identification of PFO-strokes may be of additional value. Further, PFO may remain contributory to the stroke risk in the elderly, in association with vascular risk factors.

Introduction

Patent foramen ovale (PFO)-stroke, a form of cryptogenic stroke, is typically defined by young age, a cortical lesion, and absence of vascular risk factors [1, 2]. This profile is reflected in the Risk of Paradoxical Embolism (RoPE) score, which

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predicts PFO causality in stroke [2]. Outside this score, posterior circulation predominance, multiple and small-sized lesions, and abnormal coagulation have been reported to be PFO-stroke identifying features [3–5]. However, other reports provide conflicting data suggesting anterior circulation predominance and single rather than multiple lesions in PFO-strokes [6, 7]. We hypothesize that there might be variations in PFO-stroke imaging appearance, depending on age.

Methods

We conducted an observational retrospective study at Seoul National University Hospital (SNUH) with the approval of the hospital's Institutional Review Board (IRB No: 2103-221-1210). Written informed consent was waived by the same body, as the study involves no more than minimal risk to patients. The SNUH Stroke Registry was consulted to select acute stroke and transient ischemic attack (TIA) patients from January 2010 to November 2021, who had symptom onset <7 days prior to admission and underwent a transcranial Doppler (TCD) saline agitation test (n = 1,700).

After excluding cases of large artery atherosclerosis, high-risk cardioembolism, small vessel occlusion and other determined causes, cryptogenic strokes, and TIAs (n = 533) were isolated. Any PFO presence on echocardiography was considered a medium-risk cardioembolic source and labeled cryptogenic. By Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, this cryptogenic group comprised strokes (a) with an identified medium-risk cardioembolic source or (b) of undetermined etiology despite a thorough evaluation [8, 9]. Regarding the extent of diagnostic evaluation, it is a common practice in our hospital to perform more advanced investigations when primary tests are negative, following recent stroke guidelines [9]. In most such cases, 24-h Holter monitor is additionally requested, particularly among non-lacunar strokes [10]. Cardiac CT scan (including the aorta), transesophageal echocardiography (TEE), and tumor markers are occasionally requested, depending on the clinical scenario. If these diagnostics are negative, the patient is considered to have a cryptogenic stroke, and we included such patients in this study. Excluding TIA patients, 462 cryptogenic strokes were available for analysis (shown in online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000539535).

PFO-strokes were then identified by the presence of more than 10 microembolic signals (MESs) on TCD saline agitation test, during the resting state and/or post-Valsalva maneuver. In our center, TEE, a diagnostic test that confirms a PFO by direct visualization, is not routinely performed in all cryptogenic strokes. Alternatively, MES counting by TCD is a reliable screening method for PFO detection [11]. Further, our chosen embolic cut-off was based on a meta-analysis showing increased TCD specificity for an intracardiac right-to-left shunt with MES criteria >10, compared to MES >1 (1 MB: 0.89 [0.82–0.96]; 10 MB: 1.00 [1.00–1.00]; p value = 0.04) [12].

In our hospital's protocol, MESs are counted thru insonation of both middle cerebral arteries, during resting and Valsalva states, using a TCD monitoring device (Spencer; PMD 150, USA) with two 2 MHz probes. A contrast agent consisting of 9 mL saline:1 mL air mixture is agitated vigorously for 10 times and then injected. The presence of resting MES is observed for 60 s. Regardless of the findings, contrast agent is again injected and the patient performs the Valsalva maneuver for 10 s. MES on Valsalva state is counted for another 60 s. Resting MES is graded based on a simplified Spencer's criteria: grade I (<10 MES); grade II (10–100 MES); grade III (showering).

Several clinical and imaging variables were collected. Imaging characteristics (lesion side, number, size, pattern) were described based on the diffusion-weighted imaging sequence of brain magnetic resonance imaging. Lesion side was decided by vascular territory involvement and determined as anterior circulation, posterior circulation, or mixed [13]. Lesion number was either single or multiple, while lesion size was either small or large (<15 mm or >15 mm diameter). Stroke pattern was described as small single, multiple scattered, or large territorial lesions.

PFO- and non-PFO-strokes were compared, with and without age considered. Age grouping was either young or elderly (<70 or ≥70 years). Categorical and continuous data were reported as proportions and median (interquartile range), respectively. Wilcoxon rank sum test, χ^2 test, or Fisher's exact test determined significant differences in the measured variables, as applicable. To assess the independent association of age with PFO-stroke lesion characteristic, multivariate binary logistic regression was performed, with adjustment for the following factors: sex, National Institutes of Health Stroke Scale (NIHSS) score, body mass index, history of previous stroke, coronary artery disease, hypertension, diabetes, hyperlipidemia, and smoking. p values <0.05 meant statistical significance. All statistical analyses were conducted using R for Windows, version 4.1.3.

Results

The analysis included a total of 462 cryptogenic strokes (median age: 65.0 [55.0; 73.0]; PFO-stroke: 30.5% [141/462]; non-PFO-stroke: 69.5% [321/462]) (shown in online suppl. Table 1). Compared to non-PFO-strokes, PFO-strokes had significantly lower NIHSS scores (2.0 [1.0; 4.0] vs. 3.0 [1.0; 6.0], p = 0.001) and were more likely activity-related. The two groups, however, were similar in terms of sex, age, body mass index, and stroke lesion pattern. Notably, RoPE scores were similar in the compared groups (4.0 [3.0; 5.0] vs. 4.0 [3.0; 5.0], p = 0.790). Vascular risk factor profiles were also comparable in the two groups, except for coronary artery disease which was more frequent among non-PFO-strokes (13.7 vs. 5.7%, p = 0.018). Laboratory values were mostly comparable except for hs-C-reactive protein which was higher in non-PFO-strokes.

When all cryptogenic strokes were stratified by age, significant differences in the lesion number, pattern, and side were observed (shown in Fig. 1, online suppl. Table 2). A single (72.8 vs. 57.9%, p = 0.020) and a small single lesion (51.1 vs. 35.5%, p = 0.039) defined the young PFO-strokes, while mixed territory lesions were more common in the elderly PFO-strokes (30.6 vs. 8.9%, p = 0.001). Activity-related stroke was identifying for the young PFO-stroke compared to its non-PFO counterpart (82.6 vs. 68.0%, p = 0.035). Milder neurological deficits among PFO-strokes persisted irrespective of age, compared to non-PFO-strokes.

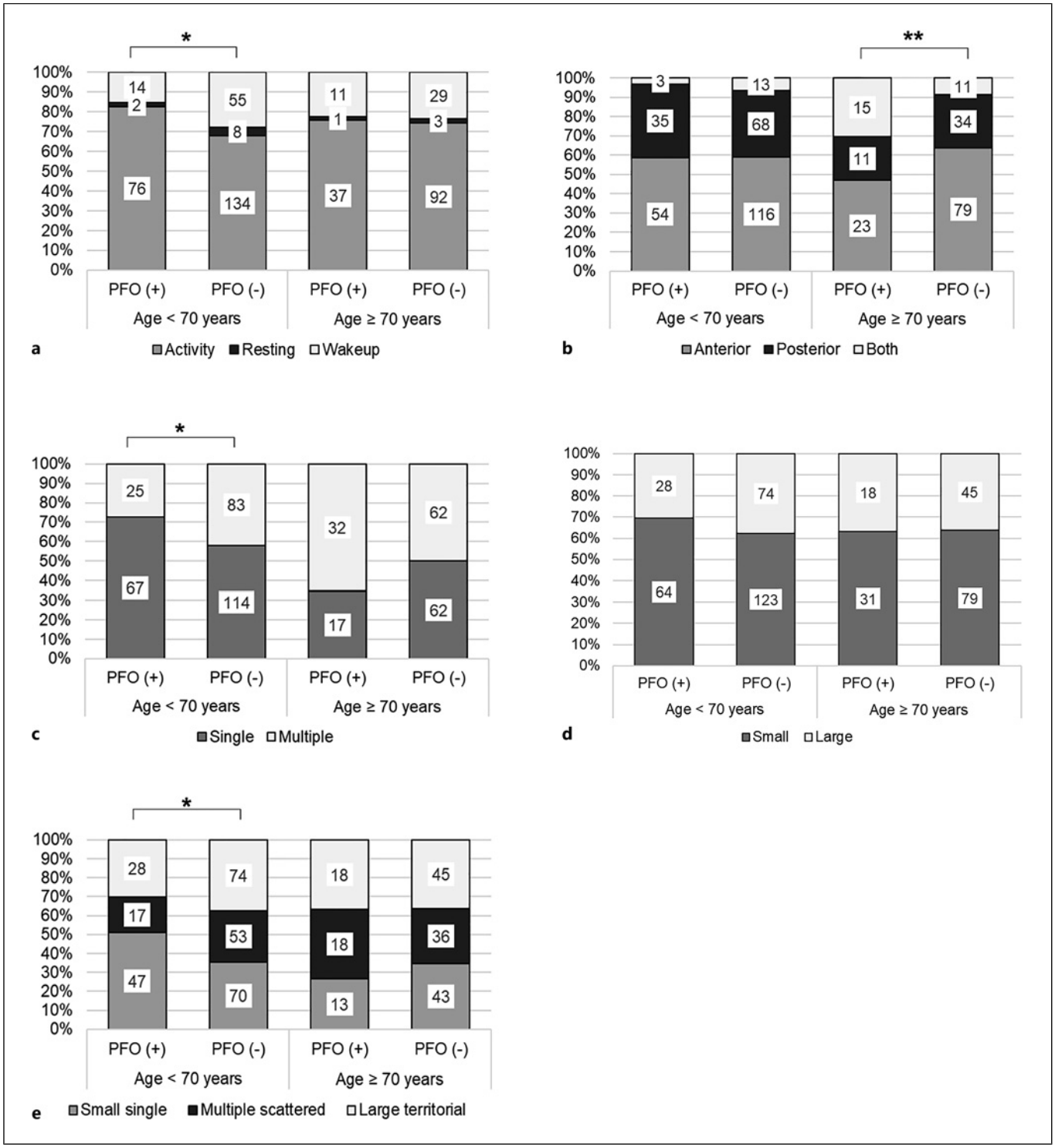

Fig. 1. Association of age with patterns of PFO-strokes versus non-PFO-strokes. **a** Situation at stroke onset. **b** Lesion side. **c** Lesion number. **d** Lesion size. **e** Lesion pattern. * means $p < 0.05$, ** means $p < 0.01$, and *** means $p < 0.001$.

Table 1. Univariate and multivariate binary logistic regression analysis of the association of age with neuroimaging parameters in PFO-associated strokes

	Univariate		Multivariate					
			model 1		model 2		model 3	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Lesion side; anterior or posterior alone (ref.) versus mixed	1.10 (1.04–1.17)	0.001	1.10 (1.04–1.17)	0.001	1.11 (1.04–1.17)	0.001	1.12 (1.05–1.20)	<0.001
Lesion number; single (ref.) versus multiple	1.05 (1.02–1.08)	0.003	1.05 (1.02–1.09)	0.003	1.06 (1.02–1.09)	0.002	1.06 (1.02–1.10)	0.005
Lesion size; small (ref.) versus large	0.99 (0.96–1.02)	0.623	0.99 (0.96–1.02)	0.608	0.99 (0.97–1.02)	0.726	1.00 (0.97–1.04)	0.909
Lesion pattern; small single (ref.) versus multiple scattered or large territorial	1.01 (0.99–1.04)	0.328	1.01 (0.99–1.04)	0.363	1.02 (0.99, 1.05)	0.295	1.02 (0.98–1.05)	0.334

Model 1: adjusted for sex. Model 2: adjusted for model 1 plus NIHSS scores. Model 3: adjusted for model 2 plus body mass index, history of previous stroke, coronary artery disease, hypertension, diabetes, hyperlipidemia, and smoking. OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale.

When PFO-strokes alone were analyzed by age, the elderly group displayed lower RoPE scores (3.0 [2.0; 3.0] vs. 5.0 [4.0; 6.0], $p < 0.001$). More notably, significant findings relating to lesion number, pattern, and side were apparent (shown in online suppl. Table 3). Young PFO-strokes were likely to display single lesions (72.8 vs. 34.7%, $p < 0.001$), while elderly PFO-strokes had more of the multiple (65.3 vs. 27.2%, $p < 0.001$) and multiple scattered lesions (36.7 vs. 18.5%, $p = 0.010$), belonging to mixed territories (30.6 vs. 3.3%, $p < 0.001$). Representative cases are depicted in online supplementary Figure 2. By multivariate logistic regression analysis, age affected lesion side (odds ratio 1.12 [1.05–1.20], $p < 0.001$) and lesion number (odds ratio 1.06 [1.02–1.10], $p = 0.005$) in the fully adjusted models (shown in Table 1).

Discussion

Our data revealed some significant associations pertaining to age. It was determined that young PFO-strokes typically had single lesions, while elderly PFO-strokes had multiple lesions of mixed arterial territories. This mixed territory pattern seen in the elderly PFO group is suggestive of an embolic process. Paradoxical embolism is the most recognized mechanism underlying PFO-strokes. Other factors have also been cited to be contributory, such as in-situ clot formation in the left atrium and a hypercoagulable status [14]. We speculate that heightened coagulability in advanced age [15, 16] with a resultant increase in thrombus burden contributes to the multiple, disseminated lesions among elderly PFO-strokes, like that of cancer-related strokes [17].

Remarkably, RoPE scores were similar between PFO-strokes and non-PFO-strokes, which is likely due to their similar age and vascular risk background. In the RoPE scoring, younger age and absence of vascular risk factors result in higher scores, suggesting PFO causality for stroke. The equally low score gained by PFO-strokes implies that this group is not necessarily defined by young age and a "healthy" vascular profile. Thus, it is possible that among the elderly, PFO may still contribute to stroke risk in association with vascular risk factors. Recent observational studies provide evidence supporting this hypothesis. According to Mazzucco et al. [18], the association between cryptogenic stroke and PFO exists even in the elderly, which by their definition pertained to those above 60 years of age. In a separate study by the same authors, higher stroke recurrence was observed among PFO subjects aged 65 years and older [19]. In comparison, our analysis used a higher age cut-off (70 years) to define advanced age. This was based on the age component of the ROPE score, wherein above 70 years is considered negligible hence not scored. Therefore, our findings could be useful when reconsidering a PFO diagnosis among patients with low ROPE scores owing to advanced age.

We acknowledge several limitations that could have resulted in selection bias, mostly related to the retrospective nature of this study. First, identification of PFO-strokes was solely based on MES counting by TCD saline agitation test. It may be difficult to fully determine whether it is a PFO-related stroke using the TCD test alone. While transthoracic echocardiography was done in almost all patients (97.0%), TEE was performed in only about half of the patients (48.1%). The latter would have been most informative, revealing high-risk PFO features, namely, shunt size and atrial septal aneurysm.

Second, as previously mentioned, extended investigations in select patients are occasionally performed in our center to determine covert stroke etiologies such as occult atrial fibrillation, aortic arch plaques, and cancer-related stroke. However, we recognize that our study population consisted of cryptogenic patients who were not uniformly examined, owing to the retrospective design of our study. In particular, the extent of advanced diagnostics was determined variably by the attending neurologist, who would have considered individual patient factors such as age and comorbidities.

Third, investigations to exclude extracardiac shunts (i.e., chest computed tomography) were not uniformly pursued to identify the truly PFO-strokes. We also recognize that MES detection time (i.e., within 15 s) increases specificity of PFO diagnosis (vs. other diagnosis) [20]. Including these criteria would have been ideal, but not possible due to the study's retrospective design. By protocol, the practice in our laboratory is to observe for MES within 60 s post-contrast injection. However, our database does not provide information as to when the first MES is observed. Lastly, while we suggested that our findings are related to differences in coagulation status across age groups, this needs objective confirmation and clarification as to what degree.

Conclusions

In summary, our observational data suggest age-specific differences in PFO-stroke imaging features. Incorporating age-specific imaging criteria in the identification of PFO-strokes may be of additional value. Further, it was demonstrated that PFO may remain contributory to the stroke risk in the elderly, in association with vascular risk factors.

Statement of Ethics

This observational retrospective study was approved by the Institutional Review Board (IRB No: 2103-221-1210) of Seoul National University Hospital (SNUH). The need for written informed consent was waived by the same body, as the study involves no more than minimal risk to patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.T.S.P. performed literature review, interpreted results, and wrote and edited the manuscript. H.-Y.J. performed statistical analyses, interpreted results, created figures, and wrote and edited the manuscript. K.-H.J. conceptualized the study, reviewed the literature, performed statistical analyses, interpreted results, and edited the manuscript. S.Y.H. conceptualized the study, reviewed the literature, collected the data, and performed statistical analyses. E.-J.L., W.Y., D.-W.K., J.-M.K., and S.-H.L. interpreted results and edited the manuscript. All authors approved the manuscript.

Data Availability Statement

Data supporting our study findings are included within the paper. Access to supplementary data is also included. Further inquiries can be directed to the corresponding author.

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