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Original article

CLINICAL PATTERN IN PFO-ASSOCIATED STROKE

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Abstract

Patent foramen ovale (PFO) has been documented as a cause of stroke in young patients. The aim is to determine the prevalence, clinical pattern and trigger factors in young patients with PFO-associated stroke.

We prospectively examined the prevalence of PFO–associated stroke in 95 consecutive patients, aged ≤57 years with stroke/TIA, its clinical and imaging characteristics, and relationship with physical activity - induced Valsalva trigger factors.

PFO was detected in 56.6% of patients with cryptogenic stroke (CS)/TIA and in 18.18% of patients with stroke/TIA with a known cause, and CS/TIAs with PFO were significantly more often localized in the vertebrobasilar circulation compared to strokes/TIA without a PFO (60% *vs* 30.43%; p=0.03). Exposure to physical activity as a trigger factor was significantly associated with the presence of PFO compared to patients without PFO (37% *vs* 8.33%, p=0.023). RoPe score ≥7 was obtained in 73.33% of patients with CS/TIA. In 96.67% of patients with right to left shunt detected on Bubble-cTCD with CS/TIA, a PFO was confirmed by TEE and percutaneous PFO closure was performed in 73.33% of patients.

Our results suggest that there is a large proportion of patients with PFO and CS/TIA, with the likelihood that PFO in their case is etiologically related to stroke. We showed that physical activity - induced Valsalva could provoke an asymptomatic PFO to become pathological, causing PFO-associated stroke in young adults, more likely in the vertebrobasilar circulation.

Keywords: PFO; cryptogenic stoke; trigger factors

Introduction

In young patients, half of strokes are cryptogenic[1] and patent foramen ovale (PFO) occurs in 40-56% in patients <55 years old with cryptogenic stroke or transient ischemic attack[2-4]. The term PFO-associated stroke as a distinct causative mechanism of stroke has been recently proposed and it refers to "all patients presenting with superficial, large deep, or retinal infarcts in the presence of a medium-risk to high-risk PFO and no other identified

likely cause", in order to optimize patient selection for PFO closure[5,6]. The most acceptable mechanism by which PFO causes stroke is paradoxical embolism mechanism. The first case of paradoxical embolization was reported in 1877 by Julius Cohnheim in which he described a fatal case of young woman with paradoxical embolization to the middle meningeal artery arising from the femoral vein, "and what I found next I never thought of, to put these two together, until I had a close look at the heart. I found a very large foramen ovale through which I could pass three fingers with ease"[7]. Later in 1880, a manuscript by Moritz Litten presented a description of the clinical and postmortem findings of a case of paradoxical embolization to the lower extremity[7].

It is still questionable whether PFO is incidental finding or a cause of stroke. The Risk of Paradoxical Embolism (RoPE) score and PFO-associated stroke causal likelihood [PASCAL] classification[8] has been designed for this reason, to estimate the likelihood that the PFO is causally related to stroke. The transition of a PFO present from birth to a PFO causing stroke in selected patients suggests the possible presence of trigger factors that could play a role in PFO-associated stroke. In addition, it is known that PFO-related stroke is usually presented with mild stroke, as a single cortical or multiple small ischemic lesions in the vertebrobasilar circulation[9].

The aim of our study was to show the prevalence of PFO in cryptogenic stroke compared with stroke of known cause, to determine the PFO-associated stroke and present its clinical and imaging pattern. We investigated the possible relationship with physical activity – induced Valsalva trigger factors in young patients with a PFO-associated stroke.

Materials and methods

We enrolled 95 consecutive eligible patients, 18 to 57 years old, attending neurological unit in the City General Hospital "8th September"-Skopje, with an acute ischemic stroke or transient ischemic attack (TIA), or at 1-month follow-up after an inpatient admission from 01.02.2023 to 01.02.2024. Patients were eligible for enrolment if they had a diagnosis of TIA or mild to moderate stroke according to National Institutes of Health Stroke Scale (NIHSS <15) and were able to undergo contrast enhanced color - transcranial Doppler sonography (Bubble - cTCD). Written informed consent was obtained from each patient, or permission was obtained from relatives in case the patient could not provide consent. The study was approved by the local ethics committee.

We systematically collected demographic data, atherosclerotic risk factors (i.e., sex, history of hypertension, smoking, hypercholesterolemia, or diabetes), history of coronary vascular disease, history of deep vein thrombosis, stroke characteristics and severity (NIHSS), neuroimaging data, and recorded questionnaire of eventual exposure to trauma and immobilization within 1 month before stroke or physical activity - induced Valsava trigger factors (intense pushing or heavy lifting) just prior to, or during symptom onset.

Standard diagnostic tests were performed in all patients: 12-lead electrocardiography, blood testing (i.e. full blood count, C-reactive protein, lipid profile, renal function, liver and thyroid function, electrolytes, and hemostasis), cranial computed tomography, magnetic resonance imaging of the brain with TOF angiography, duplex sonography of the extracranial arteries, and CT angiographic imaging of the extracranial and intracranial arteries. For standard diagnostic evaluations, all patients underwent transthoracic echocardiography and 24-hour ECG Holter monitoring; additional diagnostic tests for vasculitis and thrombophilia screening, and genetic tests were performed in all patients.

After standard and additional diagnostic procedures, we classified the cause of stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[10] before Bubble-cTCD was performed, and divided patients into two groups according to the cause of stroke: stroke/TIA of determined known cause and stroke/TIA of unknown cause or

cryptogenic stroke. Strokes classified as event of determined cause were categorized as large vessel atherosclerotic or atheroembolic small vessel disease, cardioembolic stroke, infarcts resulting from other determined causes or multiple known causes. Patients who could not be classified into these subtypes despite extensive diagnostic testing were classified as having stroke of undetermined cause, or cryptogenic stroke. Bubble-cTCD sonography was done according to the Consensus Conference of Venice[11] by an experienced operator. If a temporal bone window was not suitable for monitoring, the basilar artery was monitored through a transoccipital approach[12]. We used the Spencer logarithmic scale[13] (SLS) to assess the size of shunting. According to the SLS, a grade of ≥3 was used as a clinically significant and positive finding for right-to-left shunt (RLS) in our study.

For further evaluation in patients, transesophageal echocardiography (TEE) was performed for diagnosis and detailed evaluation of PFO characteristics. In order to determine the PFO relationship to stroke, in all patients with cryptogenic stroke and PFO we estimated the RoPe score and PASCAL classification, and after complete work-up for exclusion of other causes of stroke, we accordingly classified the stroke into PFO-associated stroke for further percutaneous PFO closure.

Statistical analysis

Categorical variables are shown with absolute and relative numbers. Numerical (quantitative) variables are shown with average, standard deviation, minimum and maximum values, median value and interquartile rank. Proportions between groups were compared by the X2 test. Chi-square and Fisher's exact test were used to compare qualitative variables. Logistic univariate and multivariate regression analysis, with calculation of the odds ratio and 95%CI was used to determine the independent prognostic value of cryptogenic stroke in predicting the presence of PFO. Statistical analysis of data obtained in the study was done with the statistical SPSS 23.0 program.

Results

Out of 95 patients, nine were excluded from analysis because Bubble-cTCD could not be performed due to non-cooperation in performing the Valsava maneuver, and 86 patients were further evaluated in our study. The age range of patients was 20-57 years (mean 42.2 ±8.3) and 8.14% of patients had TIA. Stroke was classified as cryptogenic in 53 of 86 patients (61.63%). The most common cause of stroke were other known causes of stroke (dissection of carotid and vertebral arteries, vasculitis, inflammation, malignancy, coagulopathy, etc.) including 17 (51.51%) patients; there were no patients with cardioembolic stroke/TIA as a result of atrial fibrillation (Figure 1).

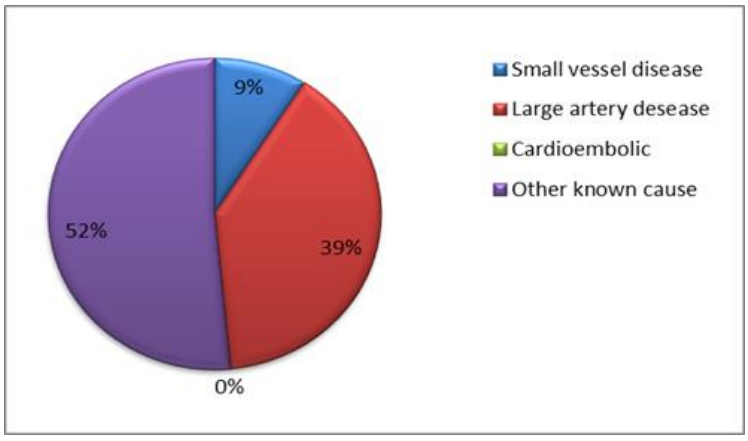


Fig. 1. Subtype of stroke in patients with stroke of known cause

A significantly higher prevalence of PFO in patients with cryptogenic stroke/TIA compared to patients with stroke/TIA of known cause was registered. PFO was detected in 56.6% of patients with cryptogenic stroke/TIA and in 18.18% of patients with stroke/TIA with a known cause (Figure 2). In the unadjusted univariate regression analysis, the odds ratio was 5.870 (95% Confidence interval 2.079-16.574, p<0.0001), in the adjusted regression analysis for age, hypertension, coronary disease it was 4.012 (95% Confidence interval 1.323-12.171, p=0.014), indicating that patients with cryptogenic stroke/TIA compared to those with stroke/ TIA of known causes had an approximately 4-fold higher probability of PFO occurrence. Multivariate analysis showed that the existence of a PFO was independently associated with cryptogenic stroke/TIA.

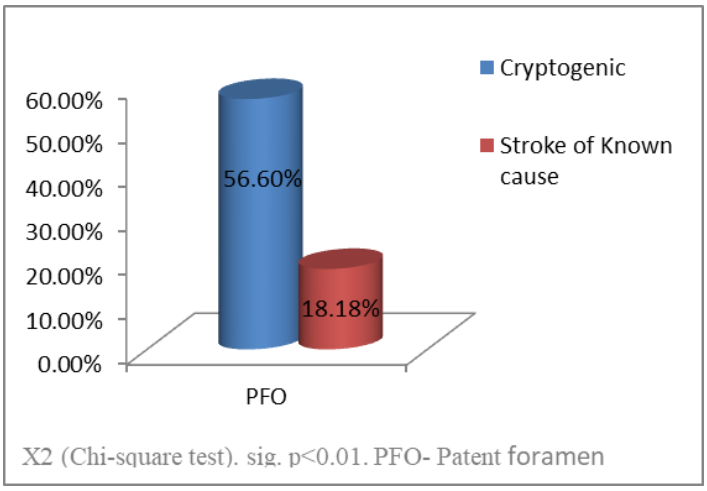


Fig. 2. Prevalence of PFO in patients with cryptogenic events compared to patients with events of known cause

Patients with cryptogenic stroke/TIA had a lower prevalence of hypertension, diabetes mellitus, hyperlipidemia and history of coronary artery disease (Table 1). There were no significant differences between the two groups with regard to sex or the presence of history of smoking. Among patients with cryptogenic stroke/TIA, a statistically significant difference in smoking status was confirmed (p=0.028); there was a significantly smaller number of smokers among patients with PFO (26.67% *vs* 56.52%). High blood pressure was significantly less common in patients with cryptogenic stroke/TIA and PFO compared to patients without PFO (16.67% *vs* 52.17%; p=0.0061). Hyperlipidemia was significantly less common in patients with PFO than in patients with cryptogenic stroke/TIA without PFO (16.67% *vs* 56.52%; p=0.0024). Among patients with cryptogenic stroke/TIA, only patients with PFO had history of deep vein thrombosis, 13.333%, but the differences compared to patients without PFO were not sufficient for statistical significance. There were no differences regarding the history of coronary artery disease and diabetes mellitus.

The NIHSS score had similar values in cryptogenic stroke patients with and without PFO (p=1.0). The mean NIHSS score was 5.47 ± 2.5 in patients with PFO and 5.78 ± 3.3 in patients without PFO. Significantly lower NIHSS score (p=0.01) was confirmed in patients with cryptogenic stroke/TIA compared to patients with stroke/TIA of known cause. The mean NIHSS score was 5.49 ± 2.6 in patients with cryptogenic stroke and 6.47 ± 2.3 in patients with stroke of known cause (Figure 3).

Table 1. Baseline characteristics in patients with cryptogenic versus stroke/TIA of known cause and in patients with cryptogenic stroke/TIA with PFO versus without PFO

	Stroke/TIA Cryptogenic (n=53)	**Stroke of known cause (n=33)**	**p-level**	**Cryptogenic stroke/TIA PFO (n=30)**	**Without PFO (n=23)**	**p-level**
Age	41.47±7.8	43.42±8.4	0.28			
Female	26 (49%)	12 (36%)	0.25			
Male	27 (50.9%)	21(63.6%)				
Hypertension	17 (32.1%)	24(72.7%)	***0.00024	5(16.67%)	12(52.17%)	**p=0.0061
Hyperlipidemia	18(34%)	21(63.6%)	**0.0072	5(16.67%)	13(56.52%)	**p=0.0024
Coronary artery disease	0	2(6.1%)	0.14	0	0	
Diabetes mellitus	3(5.7%)	8(24.2%)	*0.019	0	3(13.04%)	p=0.076
History of smoking	21(39.6%)	18(54.6%)	0.18	8(26.67%)	13(56.52%)	*p=0.028
History of deep vein thrombosis				4(13.33%)	0	p=0.124

Data are mean (SD) or n (%), X2 (Chi-square test), *sig p<0.05, Fisher's exact test, PFO-Patent foramen ovale

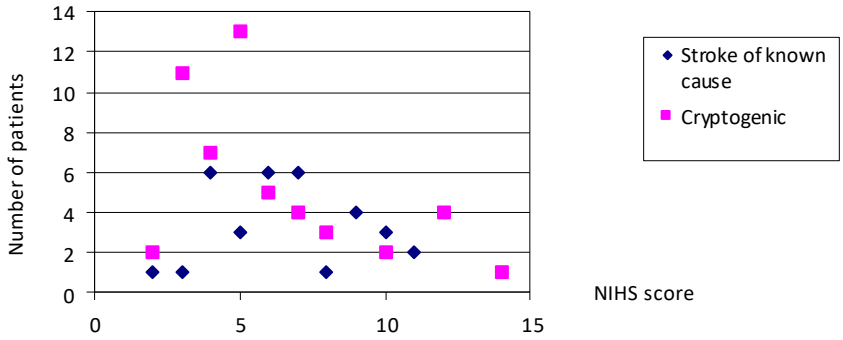


Fig. 3. Distribution of NIHSS score among patients with cryptogenic and stroke/TIA of known cause

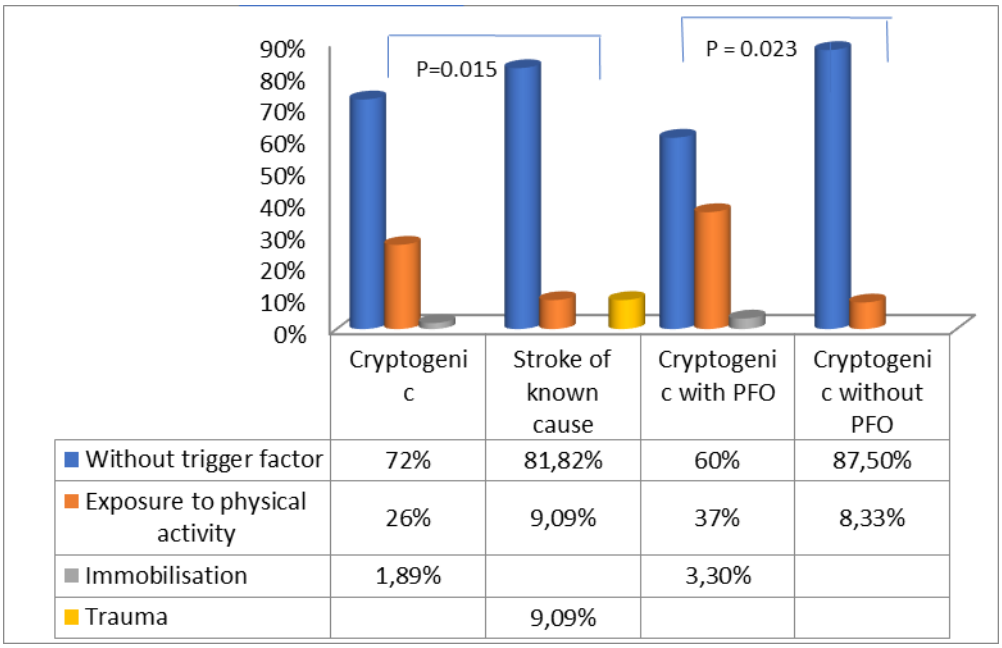
Cryptogenic strokes/TIAs with PFO were significantly more often localized in the posterior (vertebrobasilar) circulation compared to strokes/TIA without a PFO (60% *vs* 30.43%; p=0.03). Localization in the anterior (carotid) circulation had 40% of cryptogenic strokes with and 69.57% without PFO. Strokes with a known cause with and without PFO did not differ significantly in terms of localization in the imaging pattern. Strokes with a known cause with PFO were insignificantly more often localized in the anterior circulation (66.67% *vs* 44.44%), in the posterior circulation strokes were insignificantly more often without PFO (55.56% *vs* 33.33%).

Table 2. Imaging pattern regarding localization of stroke/TIA in patients with PFO *vs* without PFO in cryptogenic and stroke of known cause

Localization	**Cryptogenic Stroke/TIA PFO (n=30)**	**No PFO**	**p-level**	**Stroke/TIA of Known Cause PFO (n=6)**	**No PFO (n=27)**	**p-level**
Posterior-Vertebrobasilar	18(60%)	7(30.43%)	X2=4.56	2(33.33%)	15(55.56%)	Fisher's exact
Anterior-Carotid	12(40%)	16(69.57%)	p=0.03	4(66.67%)	12(44.44%)	p=0.039

X2 (Chi-square test), *sig p<0.05, PFO- Patent foramen ovale

The comparison regarding the trigger factors for the occurrence of stroke between cryptogenic and stroke/TIA with a known cause showed a similar representation of stroke symptoms without a trigger factor (71.7% *vs* 81.82%, p=0.29) and as a trigger factor immobilization of extremity (1.89 % *vs* 0, p=0.43); significantly more frequent representation of exposure to physical activity as a trigger factor in patients with cryptogenic stroke compared to patients with stroke of known cause (26.42% *vs* 9.09%, p=0.0597); significantly more prevalent trauma as a trigger factor in patients with a known cause of stroke compared to patients with cryptogenic stroke (0% *vs* 9.09%, p=0.0255). Exposure to physical activity as a trigger factor was significantly associated with the presence of PFO in patients with cryptogenic stroke and PFO compared to patients without PFO (37% *vs* 8.33%, p=0.023) (Figure 4).



	Cryptogenic	Stroke of known cause	Cryptogenic with PFO	Cryptogenic without PFO
Without trigger factor	72%	81,82%	60%	87,50%
Exposure to physical activity	26%	9,09%	37%	8,33%
Immobilisation	1,89%		3,30%	
Trauma		9,09%		

Fig. 4. Comparison regarding trigger factors for the occurrence of stroke between cryptogenic stroke/TIA of known cause and between cryptogenic stroke/TIA with PFO *vs* without PFO.

The Risk of Paradoxical Embolism (RoPe) score range in patients with cryptogenic stroke/TIA and PFO was 5-9 (mean 7.17±0.9), 22(73.33%) of patients obtained a RoPe score 7 and higher. In 96.67% of patients with right-left shunt detected on Bubble-cTCD with cryptogenic stroke/TIA, a PFO (>2 mm) was confirmed by TEE and in 3.33% of patients with cryptogenic stroke/TIA without Bubble-cTCD detected right to left shunt had a positive finding for PFO on TEE. Percutaneous PFO closure was performed in 73.33% of patients with cryptogenic stroke/TIA (Table 3).

Table 3. TEE confirmed PFO among patients with cryptogenic stroke/TIA with RLS *vs* without RLS detected on Bubble-cTCD; percutaneous PFO closure in patients with PFO-associated stroke/TIA

		Cryptogenic stroke/TIA			
		N	**RLS**	**Without RLS**	
TEE	PFO	28	27(90%)	1(3.33%)	X^2=38.32
	No PFO	25	3(10%)	22(96.67%)	***p=0.00001
Percutaneous PFO closure	Yes	22	22(73.33%)	0	
	No	31	8(26.67%)	23(100%)	

X2 (Chi-square test), * **sig p<0.0001, PFO-Patent foramen ovale, TEE-Transesophageal echocardiography, RLS-Right to left shunt

Discussion

It has been well-established for more than two decades that the prevalence of PFO in patients with cryptogenic stroke is considerably higher than that in the general population[14]. We found a higher prevalence of PFO in patients with cryptogenic stroke/TIA compared to patients with stroke/TIA of a known cause, and our results of the association between PFO and cryptogenic events were consistent with previous study who showed that the presence of PFO in patients younger than 55 years was significantly associated with cryptogenic stroke[14].

Regarding the relationship of PFO-associated stroke/TIA with essential cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, history of smoking), our study suggested that these risk factors played a small role in PFO-associated stroke, and other mechanisms were responsible for onset of stroke. Several mechanisms have been hypothesized, of which the paradoxical embolism mechanism following deep venous thrombosis is the most acceptable so far[15,16]. The present data suggests that PFO may be responsible for *in situ* thrombosis [16-19], and these data support the hypothesis of flow decline with blood stagnation and formation of thrombi within the PFO or atrial septal aneurysm[15,19]. Another hypothesis supported that embolic events in PFO, especially with septal aneurysm, are caused by atrial vulnerability induced by atrial tachyarrhythmias or paroxysmal atrial fibrillation. [20-24].

Our results showed that patients with cryptogenic stroke/TIA had a significantly less severe stroke and the neurological deficit was milder in patient with cryptogenic stroke than in patients with stroke of a known cause and similar result was obtained comparing patients with cryptogenic stroke/TIA with PFO and without PFO. A study by Lamy *et al.* (2002) also showed that patients with PFO had significantly less severe stroke as assessed by the Ranking scale. An explanation behind this might be that PFO is considered as a channel for the embolus to travel from the venous system to cerebral circulation, which can generally allow the smaller emboli to pass through[25] and PFO may work as filter, allowing only small emboli to pass through the shunt[9]. Previous study regarding the imaging features reported that small lesions were more common in cryptogenic stroke patients with PFO compared to cryptogenic stroke patients without PFO[26] and the likelihood of patients with small lesion with the increase in RLS which explains that the possible reason is that the emboli that can go through the PFO are often small[25].

Consistent with other studies, our results showed increased involvement of posterior (vertebrobasilar) circulation[9,26] in patients with cryptogenic stroke/TIA with PFO compared to patients with cryptogenic stroke/TIA without PFO. Increased frequency of PFO-associated stroke in vertebrobasilar circulation was explained by a study using radionuclide venography monitoring the passage of blood flow through PFO after Valsalva maneuver[27]. They found that during Valsalva maneuver the blood flow in posterior circulation exceeded the anterior circulation by 16.1%[27], which may explain the high frequency of lesions in the posterior circulation in PFO-associated stroke. The carotid system is being better supplied by the presence of numerous perivascular adrenergic nerves than the vertebral system[28] and therefore, during the Valsalva maneuver increased sympathetic stimuli which are less in posterior circulation, increase blood flow and the chance of blood clot formation to the vertebrobasilar circulation after passing through PFO[9].

Studies have so far reported association between trigger factors (vigorous physical exercise, sexual activity, illicit drug use, fever and flu-like disease) and ischemic stroke in young adults (<50 years)[29,30]. Limited data exists regarding the relationship between trigger factors (exercise-induced Valsalva) and PFO - associated stroke[31,32]. We found that exposure to physical activity may be a potential trigger factor for PFO-associated stroke. Physical activity - induced Valsalva during symptoms onset increased intracardiac pressure and provoked right to left shunting. Valsalva-like-straining is a known risk factor for worsening large right to left shunt, creating the terminal conditions for embolism to occur[33]. Future research should focus on why most patients with a PFO experience a stroke only once in

their life, despite the fact that most trigger factors are present multiple times throughout life and why, for example, labor does not seem to be a major risk factor for PFO-associated stroke, despite the fact that women during childbirth are in a prothrombotic state and need to exert a significant Valsalva maneuver[32]. Small PFOs are hard to be detected by TEE, and their provocation by the Valsalva maneuver is critical for detecting them[34]. However, it can be difficult to perform the Valsalva maneuver during TEE, especially in elderly patients with severe neurological deficits. Because provoked RLS is common, the TCD-PFO test plays an important complementary role to TEE and should be considered when there is suspicion for a PFO-stroke, especially if the patient performs the Valsalva maneuver poorly[35].

For a long time, many authors have tried to propose appropriate recommendations to determine whether PFO is a random finding or is related to cryptogenic stroke. So far, RoPe score and PASCAL classification which combines the RoPE score with high-risk PFO features (either an atrial septal aneurysm or a large-sized shunt), estimate the likelihood that PFO was causally related to stroke and the risk of recurrent risk within 2 years after the index event[5,8] has been designed for this reason. RoPE scale is a 10-point score determining age, hypertension, diabetes mellitus, history of stroke or TIA, history of smoking, and neuroimaging (large cortical infarct). Higher RoPE score results from young age, cortical infarcts and absence of traditional stroke risk factors; the higher the RoPE score the more likely that a PFO is pathogenic[8]. In our study, 73.33% of patients with PFO and cryptogenic stroke/TIA obtained a RoPe score of ≥7 and have >72% probability that PFO is related to stroke. Right to left shunt degree, atrial septal aneurysm and other PFO high-risk characteristics were not included in the RoPe score variables[36]. The RoPe score is a probability index; thus, low scores cannot exclude with certainty the possibility of PFO - attributable stroke, while higher scores cannot confirm the causative relationship[37]. According to the PASCAL classification system, all patients with a RoPe score of 7 and higher including high-risk PFO features had possible or probable PFO-related stroke and were referred for percutaneous catheter closure. Current guidelines for the management of patients with a PFO-associated stoke recommend performing transcatheter PFO closure over medical therapy alone for patients of 18 and ≤60 years age. But, PFO closure should be performed after detailed investigations and clinical evaluations of patients with PFO-associated stroke. A necessary multidisciplinary approach is recommended for further decision.

Conclusion

Our results suggest that there is a large proportion of patients with PFO diagnosed with cryptogenic stroke/TIA, with the likelihood that PFO in their case is etiologically related to stroke. PFO-associated stroke was frequently observed in cryptogenic stroke/TIA, and we showed that physical activity - induced Valsalva could provoke an asymptomatic PFO to become pathological, causing PFO-associated stroke in young adults, more likely in the vertebrobasilar circulation.

Conflict of interest statement. None declared.

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