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Risk profile of anatomical and functional parameters of patent foramen ovale and associated anatomical structures in patients with cryptogenic stroke or transient ischemic attack

Rizikový profil anatomických a funkčných parametrov foramen ovale patens a asociovaných anatomických štruktúr u pacientov s kryptogénnou ložiskovou ischémiou mozgu alebo tranzitórnym ischemickým atakom

Juraj Dúbrava[1], Rastislav Šidlo[2]

[1]Department of Noninvasive Cardiology, University Hospital Bratislava, Slovakia

Dubrava J, Sidlo R. **Risk profile of anatomical and functional parameters of patent foramen ovale and associated anatomical structures in patients with cryptogenic stroke or transient ischemic attack.** Cardiology Lett. 2025;34(2):84–92

Abstract. *Background:* This study evaluated the risk profile of patent foramen ovale (PFO) parameters and associated structures for cryptogenic cerebrovascular (CV) accidents.
Methods: We enrolled prospectively 1270 consecutive patients who underwent contrast transesophageal echocardiography: 702 patients with cryptogenic stroke (CS) or transient ischemic attack (TIA) and 568 controls without CV accidents. In this study, we evaluated the patients diagnosed with PFO. We compared 224 patients with CS or TIA and PFO (31.9%) to 106 controls with the incidental finding of a PFO (18.7%). Diameter and length of the PFO, large PFO (diameter ≥ 4 mm), long PFO (length ≥ 10 mm), shunt presence without Valsalva maneuver, shunt severity, atrial septal aneurysm (ASA; septal excursion ≥ 15 mm), atrial septal defect, and Eustachian valve/Chiari network were assessed.
Results: All characteristics of PFO significantly increased relative risk (RR) of CS/TIA vs population without PFO [RR (95%CI)] – PFO: 2.04 (1.57;2.66); p<0.001, large PFO: 4.99 (2.66;9.39); p<0.001, PFO with diameter ≥ median 2.4 mm: 3.20 (2.19;4.68); p<0.001, long PFO: 2.25 (1.65;3.06); p<0.001, PFO with length ≥ median 12 mm: 2.26 (1.61;3.17); p<0.001, moderate or large shunt: 2.25 (1.65;3.08); p<0.001, shunt present without Valsalva maneuver: 2.47 (1.74;3.52); p<0.001. PFO diameter ≥ median 2.4 mm and long PFO were identified in a multivariate logistic regression

From [1]Department of Noninvasive Cardiology, University Hospital Bratislava, Slovakia and [2]Faculty of Economic Informatics, University of Economics, Bratislava, Slovakia
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Corresponding author: Juraj Dúbrava, MD, PhD, FESC, Department of Noninvasive Cardiology, University Hospital Bratislava, Antolská 11, 851 07 Bratislava, Slovakia, e-mail: dubrava@pe.unb.sk

analysis as significant risk factors of CS/TIA – 2.43 (1.58;3.74) ;p<0.001 and 1.46 (1.02; 2.08); p<0.05, respectively. In contrast, ASA, PFO+ASA, atrial septal defect, Eustachian valve/Chiari network each did not increase the risk of CV accidents vs population without respective structure. *Conclusions:* Out of the PFO parameters a large diameter most significantly increased the risk of CS/TIA. Long PFO, shunt presence without Valsalva maneuver and moderate/large shunt also significantly increased the risk. The atrial septal or right atrial structures potentially associated with PFO did not increase the risk. Fig. 3, Tab. 3, Ref. 26, on-line full text (Free, PDF) www.cardiologyletters.sk
Keywords: patent foramen ovale – cryptogenic stroke – transesophageal echocardiography – atrial septal aneurysm

Dúbrava J, Šidlo R. **Rizikový profil anatomických a funkčných parametrov foramen ovale patens a asociovaných anatomických štruktúr u pacientov s kryptogénnou ložiskovou ischémiou mozgu alebo tranzitórnym ischemickým atakom.** Cardiology Lett. 2025;34(2):84–92
Abstrakt. *Ciele:* Štúdia hodnotila rizikový profil parametrov foramen ovale patens (PFO) a asociovaných štruktúr u pacientov s kryptogénnymi cerebrovaskulárnymi (CV) príhodami.
Metódy: Prospektívne sme zaradili 1 270 následných pacientov, ktorí absolvovali kontrastnú transezofágovú echokardiografiu: 702 pacientov s kryptogénnou ložiskovou ischémiou mozgu (LIM) alebo tranzitórnym ischemickým atakom (TIA) a 568 kontrol bez CV príhod. Analyzovali sme pacientov s diagnostikovaným PFO. Porovnali sme 224 pacientov s LIM alebo TIA a PFO (31,9 %) a 106 kontrol s náhodným nálezom PFO (18,7 %). Hodnotili sme šírku a dĺžku PFO, veľké PFO (šírka ≥ 4 mm), dlhé PFO (dĺžka ≥ 10 mm), skrat prítomný bez Valsalvovho manévra, závažnosť skratu, aneuryzmu predsieňového septa (ASA; exkurzie septa ≥ 15 mm), defekt predsieňového septa a Eustachovu chlopňu/Chiariho sieťku.
Výsledky: Všetky parametre PFO signifikantne zvyšovali relatívne riziko (RR) LIM/TIA vs. populácia bez PFO [RR (95 % CI)] – PFO: 2,04 (1,57; 2,66); p < 0,001, veľké PFO: 4,99 (2,66; 9,39); p < 0,001, PFO so šírkou ≥ medián 2,4 mm: 3,20 (2,19; 4,68); p < 0,001, dlhé PFO: 2,25 (1,65; 3,06); p < 0,001, PFO s dĺžkou ≥ medián 12 mm: 2,26 (1,61; 3,17); p < 0,001, stredne závažný/závažný skrat: 2,25 (1,65; 3,08); p < 0,001, skrat bez Valsalvovho manévra: 2,47 (1,74; 3,52); p < 0,001. V multivariačnej logistickej regresnej analýze sme identifikovali PFO so šírkou ≥ medián 2,4 mm a dlhé PFO ako signifikantné rizikové faktory LIM/TIA – 2,43 (1,58; 3,74); p < 0,001, respektíve 1,46 (1,02; 2,08); p < 0,05. Na rozdiel od toho ASA, PFO + ASA, defekt predsieňového septa, Eustachova chlopňa/Chiariho sieťka nezvyšovali riziko CV príhod vs. populácia bez danej štruktúry.
Závery: Spomedzi parametrov PFO najvýznamnejšie zvyšovala riziko LIM/TIA veľká šírka kanála. Riziko významne zvyšovali aj dlhé PFO, skrat bez Valsalvovho manévra a stredne závažný/závažný skrat. Štruktúry predsieňového septa alebo pravej predsiene, potencionálne asociované s PFO, nezvyšovali riziko. Obr. 3, Tab. 3, Lit. 26, on-line full text (Free, PDF) www.cardiologyletters.sk
Kľúčové slová: patent foramen ovale – kryptogénna mozgová príhoda – transezofágová echokardiografia – aneuryzma predsieňového septa

Patent foramen ovale (PFO) is the most prevalent condition that is known to lead to systemic embolization. In 2019 an interdisciplinary European position paper on the management of patients with PFO was published (1). According to this document, two questions must be answered in PFO management: 1. estimating the probability of causal relationship of a PFO with stroke/transient ischemic attack (TIA), 2. probability of stroke/TIA recurrence. Morphological and functional characteristics of PFO and associated anatomical structures play a crucial role in answering both questions.

Several studies compared the anatomy and pathophysiology of PFO and atrial septal aneurysm (ASA) in patients with cryptogenic cerebrovascular (CV) accidents and controls (2-9). However, the number of patients was relatively small (n = 23-88).

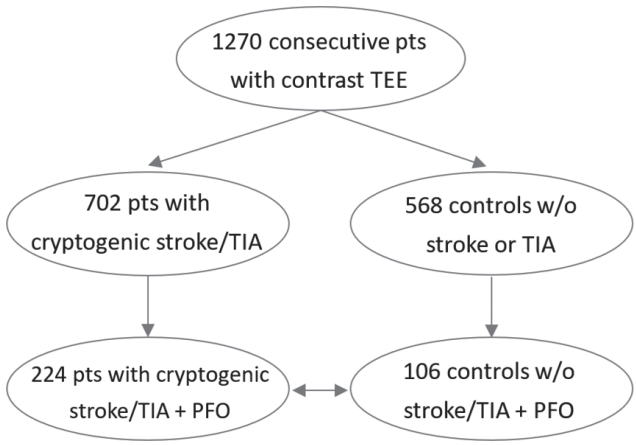

Figure 1 The study population

Therefore it is still not definitely clear whether specific parameters of the PFO and associated anatomical structures may stratify patients by the related probability that a discovered PFO is incidental or stroke related (10). It is also not known whether these parameters may reliably identify the patients at increased risk and those patients with cryptogenic stroke (CS) or TIA who might benefit from PFO closure.

The purpose of this prospective study was to assess in a larger group of patients the risk of anatomical and functional parameters of PFO and potentially associated septal or atrial structures for CS or TIA.

Methods

A total of 1270 consecutive patients underwent prospectively contrast multiplane transesophageal echocardiography (TEE): 702 patients with cryptogenic brain ischemia (582 with stroke and 120 with TIA) and 568 controls without the history of stroke or TIA.

Table 1 Baseline characteristics of patients

	Stroke/TIA + PFO (n = 224)	Controls + PFO (n = 106)	p
Male	142 (63.4 %)	45 (42.5 %)	< 0.001
Age (years)	57 ± 15*	51.4 ± 14.4**	< 0.05
Stroke/TIA	194/30 (86.6 %/13.4 %)		

PFO – patent foramen ovale, TIA – transient ischemic attack, * – median ± interquartile range, ** – mean ± standard deviation

The diagnosis of CS or TIA was made by a neurologist after excluding all definite identifiable causes.

In this monocentric study, we evaluated the patients diagnosed with PFO. We compared 224 patients with CS or TIA and PFO to 106 controls with the incidental finding of a PFO (**Figure 1**). Baseline characteristcs are given in **Table 1**. The data were analyzed for differences in diameter (i.e. size, height) and length of the PFO, presence of the large PFO, long PFO, ASA, Eustachian valve or Chiari network, shunt severity, and the right--to-left shunt via PFO presence under basal conditions (without Valsalva maneuver). The interatrial septum was investigated in the longitudinal biatrial/bicaval view and the transverse midesophageal 4-chamber view. The presence of PFO was defined as TEE evidence of right-to-left shunt of more than 3 microbubbles in the left atrium within three cardiac cycles after their appearance in the right atrium, at rest, or after Valsalva maneuver (11,12). Agitated glucose 5% solution was used in non-diabetics to detect the presence or absence of the shunt. In diabetics, agitated saline was used. The contrast was delivered into cubital veins. The degree of shunting was defined to be small if 3-9 microbubbles appeared, moderate if 10-30 microbubbles appeared, and large if more than 30 microbubbles appeared in the left atrium (13). For each patient, we calculated the separation of septum primum and septum secundum at rest, and after the Valsalva maneuver. We considered the PFO diameter as the bigger of these two values. Tunnel length was defined as the maximum overlap of the septum primum and septum secundum. The large PFO had a diameter ≥ 4.0 mm and long PFO had a tunnel length ≥ 10 mm (2,14). ASA was defined as a protrusion of interatrial septum > 15 mm into the left or right atrium or phasic excursion more than 15 mm during the respiratory cycle, with the base of the aneurysm ≥ 15 mm in diameter (15).

The study was performed according to the Declaration of Helsinki and hospital ethical standards.

Statistical analysis

Categorical data are reported as frequencies and percentages. Continuous data are presented as mean and standard deviation if normally distributed and median with interquartile range if not normally distributed. The

Table 2 Comparison of patent foramen ovale (PFO) parameters in patients with cryptogenic ischemic stroke/ transient ischemic attack (TIA) and in controls

Parameter of PFO	Stroke/TIA (n = 224)	Controls (n = 106)	p
Diameter of the channel (mm)	3.08 ± 1.99	2.33 ± 1.41	< 0.001
Large PFO (diameter ≥ 4 mm)	62 (27.7 %)	12 (11.3 %)	< 0.001
Length of the channel (mm)	13.51 ± 5.24	13.06 ± 5.76	NS
Long PFO (length ≥ 10 mm)	163 (72.8 %)	67 (66.0 %)	NS
Shunt severity	2.00 ± 0.78	1.93 ± 0.82	NS
Moderate/large shunt	156 (69.6 %)	67 (63.2 %)	NS
Large shunt	69 (30.8 %)	32 (30.2 %)	NS
Shunt present w/o Valsalva maneuver	128 (57.1 %)	50 (47.2 %)	NS

NS – non-significant

normality of the distribution of continuous variables was tested with the Kolmogorov-Smirnov test of normality. The comparison of categorical variables was performed using Pearson´s χ^2 test of independence or Fisher´s exact test. The differences between the mean values of continuous variables were compared using analysis of variance (ANOVA). Logistic regression was used to estimate the relative risk. A multivariate logistic regression model with the algorithm for stepwise regression based on Likelihood Ratio statistics was used to identify independent predictors of ischemic stroke or TIA in the study population. Correlations were analyzed with linear regression analysis and non-parametric Spearman's correlation coefficient. Differences were declared to be statistically significant at $p < 0.05$. All statistical calculations were carried out using SPSS Statistics 20.0 software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

Results

The prevalence of PFO was significantly higher in patients with cryptogenic ischemic stroke or TIA compared to the controls without the history of brain ischemia (31.9% vs 18.7%, $p < 0.0001$).

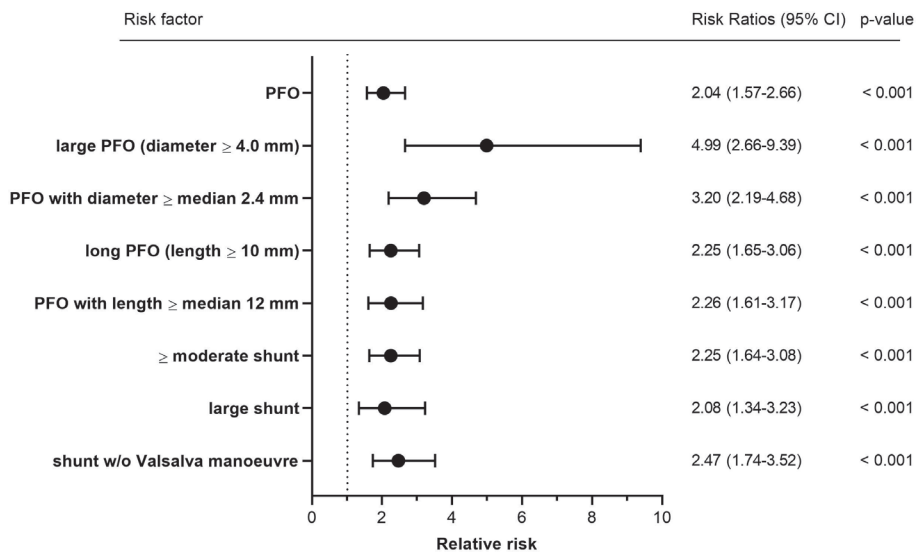

Figure 2 Risk ratio of cryptogenic stroke or TIA in patients with individual parameters of PFO compared to the population without PFO
CI – confidence interval

Table 3 Prevalence of structures potentially associated with patent foramen ovale (PFO)

Associated structures	Stroke/TIA (n = 702)	Controls (n = 568)	p
Atrial septal aneurysm	49 (7.0 %)	41 (7.2 %)	NS
PFO + atrial septal aneurysm	34 (4.8 %)	22 (3.9 %)	NS
Eustachian valve/Chiari network	71 (10.1 %)	49 (8.6 %)	NS

NS – non-significant, TIA – transient ischemic attack

Table 2 displays the comparison of the PFO parameters in patients with CS/TIA and in controls. The only parameter that significantly differed between these groups was the diameter of the PFO. Patients with brain ischemia had significantly larger PFO diameter and higher prevalence of large PFO compared to controls. Both groups did not differ in other characteristics of PFO: length, prevalence of the long PFO, shunt severity, prevalence of the large shunt or prevalence of the shunt present under basal conditions.

There was no significant difference between the patients with CS/TIA and controls in the prevalence of the ASA, ASA + PFO, Eustachian valve or Chiari network (**Table 3**). These patients did not differ in the prevalence of atrial septal defects (0.57% vs 1.41%).

As shown in **Figure 2**, all parameters of PFO significantly increased the risk ratio (RR) of CS or TIA vs the population without PFO. We found the highest RR of CS/TIA in the parameters related to the size of the PFO: large PFO (channel diameter ≥ 4.0 mm) and PFO diameter ≥ median value 2.4 mm (RR 5.0 and 3.2, respectively). The presence of PFO increased two-fold the risk of having cryptogenic brain ischemia compared to those without PFO. Other PFO parameters increased RR of CS/TIA in the range of 2.1 and 2.5 (long PFO, PFO length ≥ median value 12 mm, large shunt, shunt presence without Valsalva maneuver).

In contrast to the parameters of PFO, no anatomical structure potentially associated with PFO (ASA, simultaneous presence of ASA and PFO, Eustachian valve or Chiari network) significantly increased the risk of CS/TIA compared to patients without the respective structure. Atrial septal defect did not significantly affect the risk of cerebral ischemia either (**Figure 3**).

We performed a multivariate logistic regression model including the presence of PFO, large PFO, PFO with diameter ≥ median 2.4 mm, long PFO, PFO with length ≥ median 12 mm, large shunt, shunt present without Valsalva maneuver, ASA, PFO + ASA, and Eustachian valve or Chiari network. In this model, PFO with diameter ≥ median 2.4 mm and long PFO emerged as independent predictors of ischemic stroke or TIA in

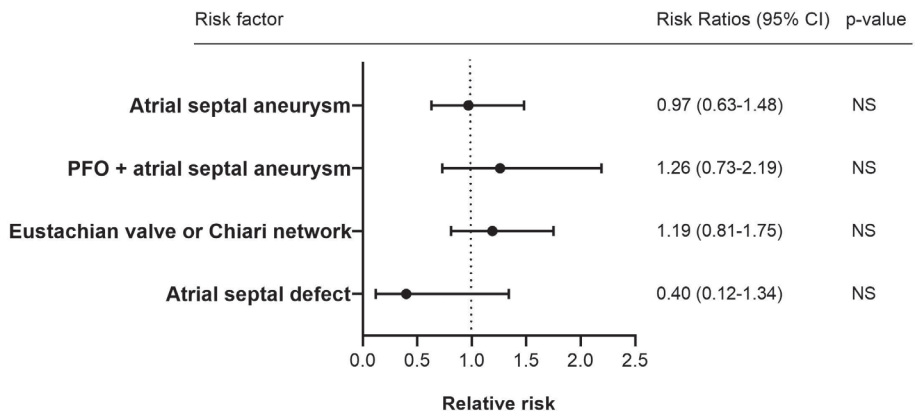

Figure 3 Risk ratio of cryptogenic stroke or TIA in patients with individual atrial septal structures or right atrial structures compared to the population without corresponding structure
CI – confidence interval

the study population of 1270 patients (RR 2.43, 95% confidence interval [CI] 1.58-3.74, p < 0.0001 and RR 1.46, 95% CI 1.02-2.08, p < 0.05, respectively).

In patients with CS/TIA, a weak but significant correlation was found between the channel diameter of the PFO and the shunt severity (r = 0.55, p < 0.0001). No significant correlation was observed between the channel length and the shunt severity.

Discussion

The main findings of our study are: 1. Among the parameters of the PFO, large diameter was the most powerful risk factor of CS or TIA vs the population without PFO. Long PFO, moderate/large shunt, and shunt present without Valsalva maneuver also significantly increased the risk. 2. Associated septal/right atrial anatomical structures were not found as risk factors of CS or TIA compared to the population without corresponding structure.

The presence of PFO itself (regardless of its features) doubled the risk of CS/TIA in our study. This finding is consistent with the analysis of Handke et al. They showed that the PFO was independently associated with CS regardless of age of the patients (16). Similarly, Cerrato et al. confirmed that PFO independently predicted an ischemic stroke or TIA (6).

Our finding on the importance of large PFO diameter correlates with the conclusions of other authors (5,17). Schuchlenz et al. found that a PFO > 4 mm was associated with an increased risk of TIA, ischemic strokes (5). Lee et al. identified 3.0 mm as the optimal cutoff value of PFO size to predict stroke recurrence within 3 years, with a sensitivity and specificity of 90.0% and 79.4% respectively (17). In contrast, Katsanos et al. in their meta-analysis of 14 prospective studies with a total of 4 251 patients with recurrent CS and TIA found that PFO size was not associated with the risk of recurrent stroke or TIA (18).

In our cohort, we also detected a large shunt as a significant risk factor for cryptogenic CV events. The same finding was identified in a meta-analysis of Hołda et al. (10).

We have also compared the parameters of PFO in patients with CS/TIA and controls. Symptomatic patients had a significantly larger PFO diameter, consistent with the findings of most other studies (2,3,5,8). Our patients with CS/TIA also had a significantly higher proportion of large PFO. The same conclusion was found by other authors (2,8). In our study, symptomatic and asymptomatic patients did not differ in the channel length or the proportion of the long PFO. Other authors found a significantly longer channel in symptomatic patients (2,8), in asymptomatic patients (4), or they found no difference (3).

In contrast to some morphological parameters, the functional parameters of PFO (shunt severity, the prevalence of the large shunt, or the shunt presence under basal conditions) did not differ in our study in patients with CS/TIA and controls. Komar et al. observed a significantly higher proportion of severe shunt via PFO in cryptogenic CV events vs controls (8). Goel et al. found only a non-significant trend towards a higher proportion of severe shunt in stroke (2). Multiple authors found that compared with controls, PFO patients with acute stroke or TIA more frequently presented with a right-to-left shunt at rest and higher membrane mobility (7,9,19).

Owing to the fact that the patient populations in various studies were heterogeneous, no universal profile of PFO risk factors was found to distinguish between patients with and without cryptogenic CV accidents. Hołda and Koziej presented the meta-analysis of 9 studies that compared parameters of PFO in cryptogenic CV accidents. No difference was found in the PFO channel length. The PFO height measured at rest did not differ between the groups but the height during a Valsalva maneuver was larger in symptomatic patients. Wessler et al. found no evidence that large PFO size, hypermobile septum, and presence of right-to-left shunt at rest are associated with clinical features suggesting that a CS is PFO-attributable (20).

We hypothesized that in patients with cryptogenic CV accidents there would be a significant positive correlation between channel diameter and the shunt severity. This correlation was significant, but weak. It is obvious that the shunt severity depends not only on the channel diameter. Schuchlenz et al. found, that in CS semiquantitative contrast correlated with PFO size only if the contrast agent was administered through a femoral vein. The correlation was poor when the contrast was

administered via a cubital vein as in our study (21). We did not find a significant correlation between channel length and shunt severity. The same finding was also presented by Kumar et al. (22).

The most striking difference between our conclusions and the literature concerns the risk of the ASA. Neither ASA nor ASA + PFO were identified as risk factors of cryptogenic CV accidents compared to the population without corresponding structure. However, several studies have confirmed the prognostic significance of the ASA (6,10,17). Lee at al. showed that ASA or hypermobile atrial septum were independent predictors of stroke recurrence in patients with PFO having CS (17). The prognostic significance of the PFO + ASA combination was also present in the study of Mas et al. The risk of recurrent stroke or TIA at four years of follow-up was 0% in patients with an ASA but no PFO, 5.6% in patients with a PFO alone, and 19.2% in patients with PFO + ASA (13). We assume that the main reason for the difference between our findings and the literature conclusions regarding the risk of ASA was its different definition in our study.

In contrast to PFO, the prevalence of associated structures (ASA, PFO + ASA, Eustachian valve/Chiari network) was almost identical in our patients with CS/TIA and controls. Previous studies have yielded conflicting results regarding the prevalence of ASA. The majority of the authors found ASA significantly more frequently in symptomatic patients (2,6,8). On the other hand, Natanzon et al. found the non-significant difference, as in our study (4). However, it should be emphasized that the definitions of ASA were not uniform. We found surprisingly almost identical occurrence of simultaneous PFO + ASA in symptomatic and asymptomatic patients. The same conclusion was also published by Cerrato et al. (6).

The clinical impact of high-risk morphology and/or a large shunt in PFO is also given by the results of interventional studies. The CLOSE trial performed in patients with CS with an ASA or a severe shunt showed that the closure of the PFO resulted in a statistically significant higher reduction of stroke recurrences as compared to medical therapy (11). Additionally, the subgroup analysis of long term RESPECT study results showed that patients with ASA or a larger shunt had a greater risk reduction with PFO closure (12).

Ahmad et al. performed the meta-analysis of 5 RCT (n = 3 440) comparing transcatheter device closure plus medical therapy and medical therapy alone in patients with CS/TIA and the PFO. The mean follow-up was 2.0-5.4 years. In patients with large shunts, PFO closure was associated with a significant reduction in stroke, whilst there was no significant reduction in a small shunt. There was no effect from the presence of ASA on recurrent stroke (23).

DEFENSE-PFO was a RCT, analyzing whether the benefits of PFO closure can be established on the basis of the PFO morphology. A total of 120 patients with CS and high-risk PFO was included. High-risk PFO was defined as PFO with ASA, hypermobility (septal excursion into either atrium ≥ 10 mm), or PFO diameter ≥ 2 mm. The primary endpoint was a composite of stroke, vascular death, or TIMI (Thrombolysis In Myocardial Infarction)-defined major bleeding during 2 years of follow-up. The closure in high-risk PFO resulted in a significantly lower rate of the primary endpoint as well as stroke recurrence (24).

The significance of the PFO parameters and associated structures is summarized in the European position paper on the management of PFO (1). Shunt severity, and atrial septal hypermobility, can be linked to a causal role of PFO. Other anatomical risk factors should also be considered, but the likelihood of a causal relationship between PFO and stroke is lower: diameter and length of the PFO channel, prominent Eustachian valve or Chiari network. Patients with PFO are at higher risk of recurrent stroke/TIA if an ASA is present. The diameter of the PFO channel should also be considered as a risk factor for recurrence (but with a lower level of risk).

Conclusion

Among the parameters of the PFO, large diameter was the most powerful risk factor of cryptogenic brain ischemia when compared to the population without PFO. Long PFO, moderate/large shunt, and shunt presence without Valsalva maneuver also significantly increased the risk. PFO diameter ≥ median 2.4 mm and long PFO emerged as independent risk factors of CS or TIA. Associated septal/right atrial anatomical structures were

not found as risk factors of CS or TIA compared to the population without corresponding structure.

Limitations

In our study, patients with cryptogenic CV accidents were significantly older and with a higher prevalence of the male gender than the controls. The age difference may be important as the interatrial septum undergoes constant, lifelong remodeling. Therefore, the size of the PFO may change over time (25). Patients with stroke and TIA were evaluated in one cohort. If we did not include patients with TIA, the results could be partially different. PFO parameters were measured by 2-dimensional (2D) echocardiography. However, PFO is a 3-dimensional structure. Therefore, it may be difficult to estimate accurate PFO morphology using 2D TEE (26). The exact definition of ASA varies according to the size. In our study, we defined ASA as a septal protrusion greater than 15 mm. However, most authors use a cut-off value of 10 mm. The hypermobile septum was not evaluated.

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References

1. Pristipino C, Sievert H, D'Ascenzo F, Louis Mas J, Meier B, Scacciatella P, et al. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. Eur Heart J 2019;40:3182-3195.
2. Goel SS, Tuzcu EM, Shishehbor MH, de Oliveira EI, Borek PP, Krasuski RA, et al. Morphology of the patent foramen ovale in asymptomatic versus symptomatic (stroke or transient ischemic attack) patients. Am J Cardiol 2009;103:124-129.
3. Bayar N, Arslan Ş, Çağırcı G, Erkal Z, Üreyen ÇM, Çay S, et al. Assessment of morphology of patent foramen ovale with transesophageal echocardiography in symptomatic and asymptomatic patients. J Stroke Cerebrovasc Dis 2015;24:1282-1286.
4. Natanzon A, Goldman ME. Patent foramen ovale: anatomy versus pathophysiology - which determines stroke risk? J Am Soc Echocardiogr 2003;16:71-76.
5. Schuchlenz HW, Weihs W, Horner S, Quehenberger F. The association between the diameter of a patent foramen ovale and the risk of embolic cerebrovascular events. Am J Med 2000;109:456-462.
6. Cerrato P, Imperiale D, Priano L, Mangiardi L, Morello M, Marson AM, et al. Transoesophageal echocardiography in patients without arterial and major cardiac sources of embolism: difference between stroke subtypes. Cerebrovasc Dis 2002;13:174-183.
7. Mesa D, Franco M, Suárez de Lezo J, Muñoz J, Rus C, Delgado M, et al. Prevalence of patent foramen ovale in young patients with cerebral ischemic accident of unknown origin. Rev Esp Cardiol 2003;56:662-668.
8. Komar M, Podolec P, Przewłocki T, Wilkołek P, Tomkiewicz-Pająk L, Motyl R. Transoesophageal echocardiography can help distinguish between patients with "symptomatic" and "asymptomatic" patent foramen ovale. Kardiol Pol 2012;70:1258-1263.
9. Nakayama R, Takaya Y, Akagi T, Watanabe N, Ikeda M, Nakagawa K, et al. Identification of High-Risk Patent Foramen Ovale Associated With Cryptogenic Stroke: Development of a Scoring System. J Am Soc Echocardiogr 2019;32:811-816.
10. Hołda MK, Koziej M. Morphometric Features of Patent Foramen Ovale as a Risk Factor of Cerebrovascular Accidents: A Systematic Review and Meta-Analysis. Cerebrovasc Dis 2020;49:1-9.
11. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al. Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke. N Engl J Med 2017;377:1011-1021.
12. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, et al. Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke. N Engl J Med 2017;377:1022-1032.
13. Mas JL, Arquizan C, Lamy C, Zuber M, Cabanes L, Derumeaux G, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 2001;345:1740-1746.
14. Kerut EK, Norfleet WT, Plotnick GD, Giles TD. Patent foramen ovale: a review of associated conditions and the impact of physiological size. J Am Coll Cardiol 2001;38:613-623.
15. Hanley PC, Tajik AJ, Hynes JK, Edwards WD, Reeder GS, Hagler DJ, et al. Diagnosis and classification of atrial septal aneurysm by two-dimensional echocardiography: report of 80 consecutive cases. J Am Coll Cardiol 1985;6:1370-1382.
16. Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. N Engl J Med 2007;357:2262-2268.
17. Lee JY, Song JK, Song JM, Kang DH, Yun SC, Kang DW, et al. Association between anatomic features of atrial septal abnormalities obtained by omni-plane transesophageal echocardiography and stroke recurrence in cryptogenic stroke patients with patent foramen ovale. Am J Cardiol 2010;106:129-134.
18. Katsanos AH, Spence JD, Bogiatzi C, Parissis J, Giannopoulos S, Frogoudaki A, et al. Recurrent stroke and patent foramen ovale: a systematic review and meta-analysis. Stroke 2014;45:3352-3359.
19. De Castro S, Cartoni D, Fiorelli M, Rasura M, Anzini A, Zanette EM, et al. Morphological and functional characteristics of patent foramen ovale and their embolic implications. Stroke 2000;31:2407-2413.

20. Wessler BS, Thaler DE, Ruthazer R, Weimar C, Di Tullio MR, Elkind MS, et al. Transesophageal echocardiography in cryptogenic stroke and patent foramen ovale: analysis of putative high-risk features from the risk of paradoxical embolism database. Circ Cardiovasc Imaging 2014;7:125-131.
21. Schuchlenz HW, Weihs W, Beitzke A, Stein JI, Gamillscheg A, Rehak P. Transesophageal echocardiography for quantifying size of patent foramen ovale in patients with cryptogenic cerebrovascular events. Stroke 2002;33:293-296.
22. Kumar P, Rusheen J, Tobis JM. A comparison of methods to determine patent foramen ovale size. Catheter Cardiovasc Interv 2020;96:E621-E629.
23. Ahmad Y, Howard JP, Arnold A, Shin MS, Cook C, Petraco R, et al. Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a meta-analysis of randomized controlled trials. Eur Heart J 2018;39:1638-1649.
24. Lee PH, Song JK, Kim JS, Heo R, Lee S, Kim DH, et al. Cryptogenic Stroke and High-Risk Patent Foramen Ovale: The DEFENSE-PFO Trial. J Am Coll Cardiol 2018;71:2335-2342.
25. Hołda MK, Koziej M, Hołda J, Piątek K, Tyrak K, Chołopiak W, et al. Atrial Septal Pouch-Morphological Features and Clinical Considerations. Int J Cardiol 2016;220:337-342.
26. Tanaka J, Izumo M, Fukuoka Y, Saitoh T, Harada K, Harada K, et al. Comparison of two-dimensional versus real-time three-dimensional transesophageal echocardiography for evaluation of patent foramen ovale morphology. Am J Cardiol 2013;111:1052-1056.