Atrial septum anatomy as a predictor of ischemic neurological episodes in patients with a patent foramen ovale

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ABSTRACT

Background: The correlation between atrial septum anatomy and the risk of ischemic neurological events remains underexplored.

Aims: This study aimed to examine both the functional and anatomical attributes of the atrial septum and identify predictors of stroke and/or transient ischemic attack (TIA) in patients diagnosed with patent foramen ovale (PFO).

Methods: A total of 155 patients diagnosed with PFO, with a cardiological cause of neurological events, were enrolled. Transesophageal echocardiography was utilized to assess the anatomy of the PFO canal, size of the right-to-left shunt, thickness of the primary and secondary atrial septum, presence of atrial septum aneurysm, and anatomical structures of the right atrium.

Results: Regression analysis showed that factors such as female sex, hypercholesterolemia, PFO canal width, and a large right-to-left shunt were significantly associated with stroke and/or TIA. Receiver operating characteristic analysis indicated that the width of the PFO canal holds a relatively weak, although significant predictive, value for ischemic neurological episodes (area under the curve = 0.7; $P = 0.002$). A PFO canal width of 4 mm was associated with 70% sensitivity and 55% specificity for predicting stroke and/or TIA.

Conclusions: The atrial septum's anatomy, especially the dimensions of the PFO canal and the magnitude of the right-to-left shunt, combined with specific demographic and clinical factors, are linked to ischemic neurological incidents in PFO patients.

Key words: atrial septum, patent foramen ovale, stroke, transient ischemic attack

INTRODUCTION

Patent foramen ovale (PFO) — a remnant of fetal circulation, present in approximately 30% of the general population is one of the potential causes of paradoxical embolism and cryptogenic ischemic stroke. Numerous studies have explored the percutaneous closure of patent foramen ovale (PFO) for the secondary prevention of stroke [1–6]. However, the criteria for patient qualification for PFO closure and the risk factors of ischemic neurological events remain areas of ongoing investigation. A pivotal consideration in this domain is the anatomical and functional characterization of PFO. Thus, we sought to examine the anatomy of the atrial septum and the PFO canal, as well as the structures of the right atrium, in relation to their potential risk of ischemic neurological events in PFO patients.

WHAT'S NEW?

One of the causes of cryptogenic ischemic stroke is a patent foramen ovale — an remnant of fetal circulation that persist in approximately 30% of the general population. Percutaneous closure of patent foramen ovale is a strategy of secondary stroke prevention. However, vast clinical heterogeneity of the target population and complex anatomy of the atrial septum make qualification for invasive treatment a challenge. In our study, we focus on clinical and anatomical details in relation to the risk of ischemic neurological events in patients with patent foramen ovale. The main conclusion from this work is that female sex, hypercholesterolemia, width, length, and magnitude of right-to-left shunt through the patent foramen ovale canal were associated with the prevalence of stroke and/or transient ischemic attack.

METHODS

Study population and design

This study constitutes a retrospective review of consecutive patients diagnosed with PFO, with cardiological causes of neurological symptoms, who were treated at our center between September 2012 and January 2014. Eligible participants had PFO, a history of cryptogenic stroke, transient ischemic attack (TIA), and/or migraine headaches, and were under 65 years of age. Exclusion criteria included known embolism causes apart from PFO, presence of atherosclerotic plaques (in the extracranial arteries, aortic arch, or ascending aorta), endocarditis, congestive heart failure, presence of other pathological intracardiac structures (like thrombus, myxoma, vegetation), diagnosed atrial fibrillation, significant mitral valve regurgitation, and presence of mitral and/or aortic valve prostheses.

Neurological events

This study was performed on a group of patients with PFO and history of neurological events: stroke and/or TIA and/or migraine. Data about neurological incidents were collected from medical records.

Imaging assessment

Transesophageal echocardiography (TEE) was carried out using a Philips iE33 ultrasound machine with a 7 MHz multiplanar transesophageal probe. Initially, patients with cardiovascular embolism with causes other than PFO were ruled out. Subsequently, the atrial septum anatomy and Chiari's network were evaluated. TEE projections used for the atrial septum assessment included middle esophageal four-chamber, middle esophageal short axis at the aortic valve, and bicaval middle esophageal views. The PFO canal width was gauged by the maximum distance between the primary and secondary septa, while the canal length was marked by the maximum overlap of the primary and secondary septal laminas. Averaged measurements across three heartbeats during the Valsalva maneuver were recorded. An atrial septum aneurysm was characterized by a deflection ≥10 mm with a 10 mm amplitude into either the right or left atria. The thickness of the primary and secondary atrial septum was measured mid-length. For contrast assessment, a mixture of 9 ml of 0.9% NaCl solution, roughly 0.5 ml of venous blood, and about 0.5 ml of air, in two 10-ml syringes, was administered into one of the cubital fossa veins. Following injection, the transit of the contrast micro-bubbles from the right to the left atrium through the PFO was assessed before, during, and after the Valsalva maneuver. The evaluation spanned three heart rate cycles after full right atrial contrast saturation. Leak size was rated on a 0–3 scale: 0 signified no left atrial passage, 1 indicated a minimal shunt with few microbubbles passing, 2 denoted a medium shunt, and 3 corresponded to a large shunt with a substantial microbubble transfer.

Statistical analysis

Quantitative variables were summarized using means and standard deviations for normally distributed data and medians alongside the first and third quartiles for non-normally distributed data. Categorical variables were represented as counts and representative percentages. The normality of data was evaluated using the Shapiro–Wilk test. Depending on data distribution, either a t-test (for normally distributed data) or a Mann–Whitney U test (for non-normally distributed data) was applied for continuous variable comparisons. Statistical analysis of data expressed on a binary scale was performed using the χ^2 test. A logistic regression model was constructed to identify predictors of neurological ischemic events. Both clinical and demographic details, along with atrial septum anatomical specifics, were incorporated into the analysis. The forward selection method was used where covariates were introduced into the model based on a significance level set at 0.05. To predict neurological incidents, receiver operating characteristic (ROC) analyses were conducted, with subsequent calculations of the area under the curve. The best cut-off point was chosen based on the shortest distance from the ROC curve to the top-left corner of the plot. The relationship between the PFO canal width and the grade of the shunt through the PFO was ascertained using the Spearman correlation test. A statistical significance threshold was set at an alpha value of <0.05. All statistical analyses were performed using SPSS Statistics 28 (IBM, Inc. NY, US).

RESULTS

A total of 155 patients participated in the study. The characteristics of the study group are outlined in Table 1. The majority of patients were female. Neurological symptoms were predominantly migraine with visual aura, observed in

Table 1. Characteristics of the study population based on history of stroke and/or transient ischemic attack

	All patients (n = 155)	Stroke and/or TIA + (n = 115)	Stroke and/or TIA – (n = 40)	*P*-value
Clinical characteristics				
Female sex, n (%)	117 (75)	79 (69)	38 (95)	<0.001
Age (years), median (Q1–Q3)	37 (28–48)	37 (29–49)	36 (27–43)	0.25
Arterial hypertension, n (%)	41 (26)	35 (30)	6 (15)	0.06
Diabetes, n (%)	0	–	–	–
Smoking, n (%)	25 (16)	20 (17)	5 (12)	0.62
Hypercholesterolemia, n (%)	23 (15)	22 (19)	1 (2)	0.009
Hormonal contraception, n (%)	35 (23)	23 (20)	12 (30)	0.2
Lower limbs varicose veins, n (%)	24 (15)	18 (16)	6 (15)	1.0
Migraine, n (%)	122 (79)	82 (71)	40 (100)	<0.001
Migraine with aura, n (%)	112 (72)	76 (66)	36 (90)	0.004
Anatomical details				
Atrial septum aneurysm, n (%)	101 (65)	77 (67)	24 (60)	0.45
Chari network, n (%)	21 (13)	14 (12)	7 (17)	0.43
PFO length (mm), mean (SD)	10.1 (3.3)	9.6 (3.2)	10.9 (3.4)	0.049
PFO width (mm), median (Q1–Q3)	4.5 (3.6–6.0)	4.9 (4.0–6.4)	3.8 (3.1–4.4)	0.002
Septum primum (mm), mean (SD)	2.2 (0.45)	2.15 (0.5)	2.3 (0.4)	0.15
Septum secundum (mm), median (Q1–Q3)	4.3 (4.0–4.9)	4.5 (3.9–5)	4.3 (4.1–4.8)	0.64
Grade 3 PFO shunt, n (%)	112 (72)	89 (77)	23 (57)	0.02

Abbreviations: PFO, patent foramen ovale; TIA, transient ischemic attack

Table 2. Logistic regression analysis of predictors of stroke and/or transient ischemic attack.

	Univariate analysis			Multivariable analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Female sex	0.12	0.03–0.51	0.004	0.08	0.01–0.70	0.02
Arterial hypertension	2.48	0.95–6.44	0.06			
Hypercholesterolemia	9.23	1.20–70.80	0.033	12.90	1.46–114	0.02
PFO canal length	0.89	0.78–1.02	0.10			
PFO canal width	1.43	1.08–1.90	0.013	1.25	0.94–1.70	0.13
Grade 3 PFO shunt	2.53	1.18–5.40	0.017	4.18	1.2–14.6	0.03

Abbreviations: CI, confidence interval; OR, odds ratio; other — see Table 1

Table 3. Multivariable predictive model for stroke and/or transient ischemic attack emphasizing patent foramen ovale (PFO) canal width

	Multivariable analysis		
	OR	95% CI	*P*-value
Female sex	0.08	0.01–0.61	0.02
PFO canal width	1.36	1.02–1.82	0.03

Abbreviations: see Table 2

72% of patients, followed by TIA in 54%, and stroke, which was the least common at 27% of the studied population. A large right-to-left shunt through the PFO canal was identified in 72% of patients (Table 1). Medium and small shunts were found in 13% and 14% of patients, respectively. Among patients with a history of ischemic neurological events (stroke and/or TIA), there were fewer women. These patients more frequently had hypercholesterolemia and large right-to-left shunts. They also had shorter and wider PFO canals as per TEE examination (Table 1).

Table 2 displays the results of logistic regression analyses focusing on identifying predictors of stroke and/or TIA. Risk factors for ischemic neurological events included hypercholesterolemia, PFO canal width, and a large shunt through the PFO. Conversely, female sex appeared to lower the risk of stroke and/or TIA. In multivariable analysis, only female sex, hypercholesterolemia, and a large shunt through the PFO were significant independent predictors (Table 2). Subsequently, we assessed the association between PFO width and the grade of right-to-left shunt. A statistically significant correlation was observed ($r = 0.318$; $P = 0.003$). As a result, a second regression analysis was performed with the PFO canal width held constant. In this analysis, both female sex and PFO canal width emerged as significant predictors of ischemic neurological events (Table 3).

In the ROC analysis, the width of the PFO canal was identified as a significant predictor of stroke and/or TIA among the study participants (area under the curve = 0.7; $P = 0.002$). A cut-off value for PFO width of 4 mm cor-

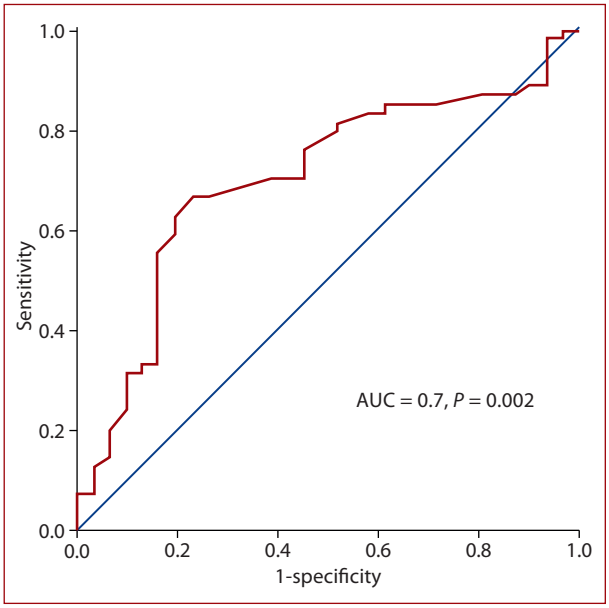

Figure 1. Receiver operating characteristic curve illustrating the predictive capacity of patent foramen ovale canal width in relation to stroke and/or transient ischemic attack

Abbreviation: AUC, area under the curve

responded with 70% sensitivity and 55% specificity for ischemic neurological events (Figure 1).

Since in this study, there was a high prevalence of females, we performed separate analyses for women, which are included in the supplementary material. Overall, we obtained similar results compared to the whole study population. The most common neurological incidents were migraine headaches (87% of patients), followed by TIA and stroke (54% and 20% of patients, respectively). A large shunt through the PFO canal was detected in 69% of patients. Medium and large shunts were observed in 15% and 16% of patients, respectively. In general, the presence of hypercholesterolemia, a wider PFO canal, and a large shunt through the PFO were associated with a higher prevalence of stroke and/or TIA in women (Supplementary material, *Tables S1–S3*). As in the case of the whole study population, in ROC analysis the width of the PFO canal was a significant predictor of the presence of stroke and/or TIA in women, yet the predictive value was relatively weak (Supplementary material, *Figure S1*). In this analysis, a cut-off value of 4 mm for PFO width was associated with 72% sensitivity and 57% specificity for stroke and/or TIA.

DISCUSSION

The anatomy of the PFO canal, including width and length, the presence of an atrial septum aneurysm, and the Chiari network, currently serve as foundational elements in assessing the risk of neurological ischemic events. Despite the significance of these elements, there is a paucity of scientific literature examining the pathophysiological implications of PFO anatomy. However, numerous anatomical-pathological studies have highlighted the varied morphology of the PFO [7–10].

Our study demonstrated that the PFO canal width was significantly larger in patients who had a history of ischemic stroke and/or TIA. In ROC analysis, the width of the PFO canal was a significant predictor of stroke and/or TIA; however, the predictive value was relatively weak. The presented results were consistent both for the general study population as well as the population limited to women, who were highly represented in our study. This aligns with previous studies which found a canal width exceeding 4 mm to be linked with elevated stroke risk [11–13]. Additionally, the magnitude of cryptogenic stroke observed on magnetic resonance imaging in PFO patients was found to correlate directly with the PFO size [14]. Some findings also suggest a relationship between the severity of stroke, clinical prognosis, and the size of PFO defect [15].

In previous reports, other anatomical aspects of the atrial septum and right atrium were analyzed in relation to the risk of ischemic stroke. One study identified an association between a thicker septum secundum and a symptomatic PFO; however, our study did not support this observation [16]. We observed no heightened ischemic neurological event risk with an increase in the thickness of the septum secundum. Several other studies argue that the presence and coexistence of an atrial septal aneurysm with a PFO heighten the risk of ischemic stroke. Our analysis did not corroborate this connection [15, 17–21]. As far as structures of the right atrium are concerned, the Chiari network incidence was 13% in our cohort, surpassing previous estimates for the general population [22]. This discrepancy might stem from our focus solely on PFO patients. While some literature implies the Chiari network plays a role in thromboembolism, infective endocarditis, arrhythmia, and lately the incidence of neurological events with PFO, our findings did not validate these views [23, 24].

Although methodologies assessing PFO shunts may differ, there is a consensus in the majority of studies on a heightened risk of significant ischemic neurological events in patients with extensive leakage through the PFO canal [9, 25, 26]. Our results mirror these findings: a larger shunt via the PFO correlated with a higher incidence of ischemic neurological events [8]. Earlier reports also emphasize the efficacy of PFO closure procedures, especially in patients with significant leakage and a concurrent atrial septal aneurysm [1–6].

Study limitations

Our study has several limitations. Primarily, the sample size of the presented analysis is relatively small. Secondly, in the analyzed population, there was a strong predominance of women, thus obtained results should be treated with caution in relation to male populations. Thirdly, the retrospective nature of the study may have introduced bias. The data regarding stroke, TIA, and migraine headaches were

sourced from medical records, which might have inherent inaccuracies. Also, since our study population had a history of neurological events, our findings might not extend to asymptomatic PFO patients. Finally, other heart structures, such as the left atrial septal pouch, which could also increase the risk of ischemic neurological events, were not assessed in this study [27].

CONCLUSION

The anatomical and functional status of the atrial septum – including the PFO canal's length and width, the grade of the right-to-left shunt, as well as demographic and clinical traits — is intrinsically linked to ischemic neurological incidents in PFO patients.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

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