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RIGHT TO LEFT SHUNT AND CRYPTOGENIC STROKE IN PATIENTS OVER 60 YEARS OLD

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ABSTRACT

Objective: To determine the possible role of patent foramen ovale (PFO) as indicated by a right to left shunt and cryptogenic stroke in patients aged ≥ 60 years and to compare the prevalence of patent foramen ovale with stroke of known cause.

Methods: We prospectively examined the prevalence of PFO using contrast enhanced colour Transcranial Doppler ultrasonography (bubble-cTCD) in 86 consecutive patients aged ≥60 years with transient ischaemic attack (TIA) or stroke and 86 consecutive patients aged <60 years with TIA/stroke as a control group. Patients with cryptogenic stroke were compared to stroke patients with known cause.

Results: A significantly higher prevalence of PFO in patients with cryptogenic compared to patients with stroke of known cause was registered in the patients aged < 60 years (56.6% vs.18.8%) and in patients aged ≥ 60 years (37.14% vs.11.76%), respectively. Multivariate analysis adjusted for age, hypertension and coronary disease showed that the existence of R-to-L shunt (RLS) was independently associated with cryptogenic stroke in both, in the younger group (odds ratio 4.012; 95% CI1.323 to 12.171, p =0.0143.70) and in the older group (odds ratio 3.197; 95% CI 1.140 to 10.877, p=0.037).

Conclusion: Our findings suggest that PFO is strongly associated with cryptogenic stroke in patients aged ≥ 60 years. Bubble – cTCD was feasible and suitable as a first-line method for the detection of PFO in older patients.

Keywords: patent foramen ovale; cyptogenic stroke; transcranial Doppler ultrasonography

INTRODUCTION

The category of cryptogenic stroke was first developed for research purposes in the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank [1] and was later modified in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) diagnostic algorithm [2]. From a clinical point of view, the term cryptogenic stroke refers to the category of ischaemic stroke for which no probable cause is found despite thorough diagnostic evaluation. However, stroke that is cryptogenic after a standard diagnostic evaluation remains a common clinical challenge, accounting for 20 to 30% of all ischaemic strokes [3].

Previous reports have shown that the prevalence of persistent foramen ovale is approximately

30% to 40% in patients with cryptogenic strokes [4] compared to approximately 25% in the general population [5]. Persistent foramen ovale (PFO) and paradoxical thromboembolism are thought to be the etiological cause in about 50% of cryptogenic strokes in young patients. A meta-analysis showed that the presence of patent foramen ovale in patients younger than 55 years old is significantly associated with cryptogenic stroke, but the relationship has remained unconfirmed in patients 55 years old or older [6]. Only a few studies have included older patients using different modality screening [7-16]. The need for more data from older patients has been highlighted [17]. Autopsy studies including healthy hearts showed that PFO size is larger in the last decades of life with an increase in mean PFO size from 3.4 mm in the first decade to 5.8 mm in the 10th decade of life [18] and the larger the PFO, the higher the risk of having a PFO-related stroke [19].

Although transesophageal echocardiography (TEE) is the gold standard for the evaluation of PFO [20,21] it is not available everywhere, it is invasive and needs sedation, which is especially difficult for elderly patients and patients with a more severe stroke. Alternatively, as a first line, especially in elderly patients, for the detection of PFO through the identification of a right-to-left shunt, an appropriate easily performed contrast Transcranial Doppler ultrasound (Bubble- TCD) can be used, which has so far shown high sensitivity and specificity for the detection of PFO in patients younger than 60 years and controls [21].

The main objective of this research was to determine whether there are significant associations between the presence of PFO and cryptogenic stroke in patients 60 years or older and to compare the findings with those for patients younger than 60 years. The aim of our study was to demonstrate that contrast enhanced colour-TCD as a non-invasive and easy-to-perform method is suitable as a first-line method for the detection of PFO as indicated by a right to left shunt in all age groups.

METHODS

STUDY POPULATION

The study included two age groups of patients, young adults <60 years old (18-59 years old) and old patients ≥ 60 years old; each group contained 86 patients in order to make a relevant comparison of the data. We enrolled from 01.02.2023 to 01.02.2024 all consecutive eligible patients up to 18 years old attending the neurological unit in General City Hospital "8th September"-Skopje, with an acute ischaemic stroke or TIA, or at 1-month follow-up after an inpatient admission. The patients were eligible for enrolment if they had a diagnosis of transient ischaemic attack or mild to moderate stroke according to National Institutes of Health Stroke Scale (NIHSS <15) and were able to undergo contrast enhanced colour-TCD (Bubble -cTCD). Because there were less younger patients and we needed more time to recruit them, we collected data from older patients first (from 01.02.2023 to 10.07. 2023) and then continued collecting data from younger patients (to 20.03.2024) until we reached the desired sample size in both groups. We excluded patients who had quantitatively or qualitatively affected consciousness, severe sensorimotor dysphasia, pregnant women and other patients who were not able to undergo Bubble - cTCD. Fourteen patients were excluded from analysis because contrast enhanced colour TCD could not be performed: 9 from the group of patients aged ≥ 60 years and 2 from the group of patients aged <60 years due to non-cooperation in performing the Valsava maneuver and 3 patients from the group aged ≥60 years had issues related to cannulation (refused or failed cannulation) due to the inability to place the contrast cannula. 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 and stroke characteristics and severity (National Institutes of Health Stroke Scale, NIHSS). 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 haemostasis), cranial computed tomography, magnetic resonance imaging of the brain with TOF angiography, or both; and duplex sonography of the extracranial arteries. Angiographic imaging of the extracranial and intracranial arteries was performed in 110 patients (64%), due to intra-arterial thrombolysis therapy or in selected patients to confirm vascular abnormalities.

For standard diagnostic evaluations all patients underwent transthoracic echocardiography and 24-hour EKG Holter monitoring. As clinically indicated, we performed additional diagnostic tests for vasculitis and thrombophilia screening, and genetic tests on patients who had cryptogenic transient ischemic attack or stroke, or those who were under 60 years old.

After extensive diagnostic procedures we classified the cause of stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [2] before contrast enhanced colour TCD was performed. In both age groups we divided patients into two subgroups according to the cause of stroke: stroke/TIA of determined known cause and stroke/TIA of unknown cause or cryptogenic stroke. Strokes classified as infarctions of determined cause were categorized as large vessel atherosclerotic or atheroembolic, small vessel disease, cardioembolic infarcts, 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 strokes of undetermined cause, or cryptogenic strokes.

TRANSCRANIAL DOPPLER SONOGRAPHY EXAMINATIONS

Contrast-enhanced color Transcranial Doppler (bubble-cTCD) sonography was done according to the Consensus Conference of Venice [22] by one experienced operator. According to the accepted guideline [23] as a contrast agent we used 9 mL of isotonic saline solution agitated with 0.5 mL of the patient's blood and 0.5 mL of air. The test was conducted on each patient at rest and with provocation, using the Valsalva maneuver or coughing. Detection of micro bubbles in the insonated middle cerebral artery after injection of the contrast (7-27 sec) was considered as a positive finding for the existence of a right-to-left shunt. If a temporal bone window was not suitable for monitoring, the basilar artery was monitored through a transoccipital approach [24]. We used The Spencer logarithmic scale [25] (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 an R-to-L shunt in our study.

STATISTICAL ANALYSIS

Proportions between groups were compared by the X2 test. 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. 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 a right-to-left shunt. The statistical analysis of the data obtained from the research was done in the statistical SPSS 23.0 program.

RESULTS

The age range of the patients in the group younger than 60 years of age was 20-58 years (mean, 45.3±8.3), and in the group of 60 years or older it was 60-88 years (mean, 70.4 ± 6.9). 8.14 % of patients younger than 60 years of age have TIA, and 12.8% of patients in the group of 60 years and older. One patient with a large R-to-L shunt reported an episode of TIA after the injection of contrast agent, during the Valsalva maneuver but without additional complications. Regarding the etiological classification, stroke was classified as cryptogenic in 88 patients (51.16%), including 53 of 86 patients younger than 60 years (61.63%) and 35 of 86 patients older than 60 years (40.70%). The difference in the distribution of patients with cryptogenic stroke/TA and stroke/TIA with a known cause between the two age groups was statistically significant (p=0.006). Cryptogenic stroke/TIA was significantly more often associated with younger age. (Table 1)

In the group with patients younger than 60 years of age, the most common cause of stroke/TIA were other known causes of stroke (dissection of carotid and vertebral arteries, vasculitis, inflammation, malignancy, coagulopathy, etc.), including 17 (51.51%) patients, whereas in the group of patients of 60 years and older, the most common cause was cardioembolic stroke as a result of atrial fibrillation, including 19 (37.25%) patients. There was a similar incidence of stroke/TIA as a result of large vessel disease in both age groups. There were no significant differences between the two groups with regard to sex or the

Table 1. *Baseline characteristics in patients with cryptogenic versus stroke/TIA of known cause*

	Age <60			Age ≥ 60		
	Cryptogenic (n=53)	Stroke of Known Cause (n=33)	p-level	Cryptogenic (n=35)	Stroke of Known Cause (n=51)	p-level
Age	41.47±7.8	43.42±8.4	0.28	66.40±4.9	73.14±6.8	<0.0001
Sex Female Male	26 (49 %) 27 (50.9 %)	12 (36 %) 21 (63.6 %)	0.25	17 (48.6 %) 18 (51.4 %)	18 (35.3 %) 33 (64.7 %)	0.22
Hypertension	17 (32.1%)	24 (72.7 %)	***0.00024	26 (74.3%)	46 (90.2 %)	*0.049
Hyperlipidaemia	18 (34 %)	21 (63.6 %)	**0.0072	6 (17 %)	33 (64.7 %)	***0.00001
Coronary artery disease	0	2 (6.1 %)	0.14	2 (5.7 %)	18 (35.3 %)	**0.0014
Diabetes	3 (5.7 %)	8 (24.2 %)	*0.019	5 (14.3 %)	23 (45 %)	**0.0027
History of smoking	21 (39.6 %)	18 (54.6 %)	0.18	11 (31.4 %)	11 (21.6 %)	0.3
Data are mean (SD) or n (%)						

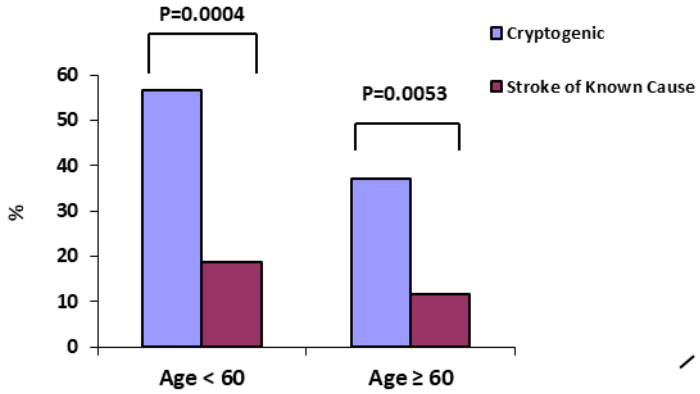
presence of history of smoking. Patients in the group younger than 60 had a lower prevalence of hypertension, hyperlipidaemia, diabetes mellitus, and a history of coronary disease compared to the group of of patients 60 years and older. Patients with cryptogenic stroke had a lower prevalence of hypertension, diabetes mellitus, hyperlipidaemia and history of coronary artery disease in both age groups. (Table 1)

A significantly higher prevalence of R-to-L shunt in patients with cryptogenic stroke/TIA compared to patients with stroke/TIA of known cause was registered in both age groups (p<0.0001). In the age group of patients aged <60 years, R-to-L shunt was detected in 56.6% of patients with cryptogenic stroke/TIA and in 18.18% of patients with stroke/TIA with a known cause. In the age group aged ≥60 years, R-to- L shunt was detected in 37.14% and 11.76%, respectively, of patients with cryptogenic stroke/TIA and stroke/TIA of known cause. (Figure 1)

Table 2 shows the results of univariate and multivariate logistic regression analysis to determine the prognostic value of cryptogenic stroke/TIA versus stroke/TIA of known cause in the occurrence of R-to-L shunt. In the unadjusted univariate regression analysis, the odds ratio for patients younger than 60 years was 5.870 (95% Confidence interval 2.079 – 16.574, p<0.0001), in the adjusted regression analysis it was 4.012 (95% Confidence interval 1.323 – 12.171, p =0.014), indicating that patients aged < 60 years with cryptogenic stroke/TIA compared to those with stroke/TIA of known causes have an approximately 4-fold higher probability of R-to-L shunt occurrence. In the unadjusted univariate regression analysis, the odds ratio for patients 60 years old and older was lower - 4.432 (95% Confidence interval 1.485 – 13.228, p=0.008), in the adjusted regression analysis it was 3.197 (95% Confidence interval 1.140 – 10.877, p=0.037), indicating that patients aged ≥60 years with cryptogenic stroke/TIA compared to those with stroke/TIA of known causes have about a 3-fold higher probability of R-to-L shunt occurrence. Multivariate analysis showed that the existence of R-to-L shunt was independently associated with cryptogenic stroke/TIA in both age groups. (Table 2)

Transthoracic echocardiographic findings showed a significant association of atrial septal aneurysm with R-to-L shunt in all patients in both the younger group (47.22% vs. 2%, P=0.00001) and in the older group (52.63% vs. 3%, P= 0.00001). (Table 3) Atrial septal aneurysm was also greater among patients with R-to-L shunt than among those without R-to-L shunt in patient with cryptogenic stroke/TIA, both in the younger group (53.33% vs. 4.35%, P=0.000015) and in the older group (84.62% vs. 13.64%, P<0.00011). (Figure 2)

Age group	RLS	Stroke/TIA			p-level
		n	Cryptogenic n (%)	Known Cause n (%)	
Age <60	yes	36	30 (56.6)	6 (18.18)	X^2=12.3
	no	50	23 (43.4)	27 (81.82)	**p=0.0004
Age ≥ 60	yes	19	13 (37.14)	6 (11.76)	X^2=7.8
	no	67	22 (62.86)	45 (88.24)	**p=0.0053



X2 (Chi-square test). **sig p<0.01. RLS= right-to-left shunt

Figure 1. *Prevalence of RLS in patients with cryptogenic events compared with patients with events of known cause, according to age group*

Table 2. *Odds ratio for presence of a R-to-L shunt among patients with Cryptogenic Stroke Versus those with Stroke of Known Cause, according to age group. Odds ratio was adjusted for age, hypertension, coronary disease*

	Univariate				Multivariate			
	p	Odds ratio	95% CI for Exp (B)		P	Odds ratio	95% CI for Exp (B)	
			Lower	Upper			Lower	Upper
All patients	Ref.gr. Stroke of Known Cause				0.001	3.949	1.802	8.653
Cryptogenic stroke	0.000	5.733	2.734	12.021				
Age <60	Ref.gr. Stroke of Known Cause				0.014	4.012	1.323	12.171
Cryptogenic stroke	0.001	5.870	2.079	16.574				
Age ≥ 60	Ref. gr. Stroke of Known Cause				0.037	3.197	1.140	10.877
Cryptogenic stroke	0.008	4.432	1.485	13.228				

Table 3. *Prevalences of atrial septal aneurysm in all patients with RLS compared with patients without RLS, according to age group.*

Age groups	IAS	RLS			p-level
		n	Yes n (%)	No n (%)	
Age < 60	Normal IAS	68	19 (52.78)	49 (98)	X^2=25.86
	Atrial septal aneurysm	18	17 (47.22)	1 (2)	***p=0.00001
Age ≥ 60	Normal IAS	74	9 (47.37)	65 (97)	X^2=30.39
	Atrial septal aneurysm	12	10 (52.63)	2 (3)	***p=0.00001

X2 (Chi-square test), * **sig p<0.0001. RLS= right-to-left shunt. IAS= Interatrial septum

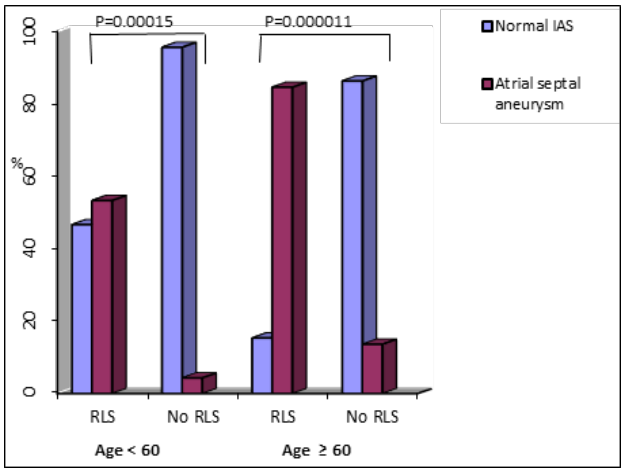


Figure 2. *Prevalences of atrial septal aneurysm among patients with RLS and those without RLS in cryptogenic stroke/TIA, according to age group.*

RLS = Right-to Left Shunt. IAS= interatrial septum

DISCUSSION

We found a higher prevalence of right-to left shunt in patients with cryptogenic stroke/ TIA compared with patients with stroke/TIA of known cause, and this association was shown in the younger age group as well as in the older age group. The results from previous studies using bubble-TCD [9,10,15] and transesophageal echocardiography studies [7,8,11,12,13,16] in older age patients were heterogenous. Most of them showed a higher prevalence of PFO in older patients with cryptogenic stroke than in those with stroke of known etiology. In a population-based study using Bubble-TCD, Mazzucco et al. reported [15] a higher prevalence of R-to-L shunt in patients with cryptogenic stroke/TIA compared to stroke of known cause, restricted to patients older than 60 years (36% and 21%). Handke et al. reported significantly greater prevalence of PFO among patients with cryptogenic stroke than among patients with stroke of known cause for patients 55 years old or older (28.3% vs. 11.9%, P<0.001) using transesophageal echocardiography [12]. Our results of the association between R-to-L shunt and cryptogenic events in patients older than 60 years were consistent with these two previous studies, further supporting the hypothesis that PFO may be a cause of stroke in older patients as well. Although elderly patients have a higher risk factor profile for ischemic stroke, those with PFO are at particularly high risk for paradoxical embolization. Some studies have shown that a tendency to venous thrombosis may increase the risk of paradoxical embolization [26], and a higher prevalence of deep vein thrombosis has been observed in some cryptogenic stroke patients with PFO [27]. Elderly patients have an increased propensity for venous thrombus formation due to the reduced levels of physical activity [28]. In addition, there are changes in endothelial and platelet function that may increase the risk for venous thrombus formation [29]. With increasing age there is also an increase in right ventricular pressure that may predispose to right-left shunting in the presence of PFO [30]. The increased presence of potentially embolic thrombotic material with the presence of R-to-L shunt in elderly patients may contribute to an increased propensity for paradoxical embolization. Older patients might be more susceptible to paradoxical embolism associated with R-to-L shunt, and some evidence suggests that the presence of PFO significantly increases the risk of recurrent ischemic stroke or death in older patients with cryptogenic events than in younger patients with cryptogenic events [17]. Previous study has shown that the presence of patent foramen ovale with concomitant atrial septal aneurysm is associated with a high risk of paradoxical embolism [31], and a high-risk characteristic in older patients as well [12]. Our data also suggest that the R-to-L shunt is associated with a concomitant atrial septal aneurysm in patients with cryptogenic stroke or TIA, particularly in the older age group.

We have shown that contrast enhanced Transcranial Color Doppler ultrasound was easy to perform and acceptable in most patients with transient ischemic attack/stroke. Systematic review from Stafford et al. showed [32] that contrast enhanced Transcranial Doppler ultrasound (cTCD) has the highest sensitivity for detecting

right-to left shunt of 91% to 100% [33-39], while the specificity rates for cTCDs were between 78% and 100%, even over 90% specificity in most studies [33,37-44]. A small proportion of R-to-L shunts is due to non-PFO sources, usually pulmonary shunts, but the majority (around 95%) of cTCD-detected R-to-L shunts are shown to be due to PFO on transesophageal echocardiography (TEE) [45,46]. TEE is still necessary for patients who require analysis of the anatomy of the defect and further treatment with an intervention to close it [47]. On the other hand, in our study a few patients from the group aged ≥60 years (13%) who did not undergo bubble-TCD were not suitable for TEE either because of non-cooperation in performing the Valsava maneuver or due to issues related to cannulation. However, although bubble-TCD is not a substitute for TEE, which is still necessary to confirm the size of the R-to-L shunt and associated interatrial septal anatomical features; the latter procedure is invasive and costly, often requires sedation, and has rare but serious complications [48]. Our results suggested that contras enhanced colour Transcranial Doppler ultrasound is a noninvasive, accurate method for detecting PFO and emphasized its role as a primary screening modality to identify the subset of patients in whom transesophageal echocardiography might be indicated. In terms of treatment, previous trials involving patients with cryptogenic TIA/stroke younger than 60 years showed a better outcome of percutaneous PFO closure compared to medical therapy alone [49-51]. Guidelines for the management of patients with a PFO-related stoke recommends performing transcatheter PFO closure over medical therapy alone for patients of 18 and ≤ 60 years age. The guidelines recommendations are currently percutaneous PFO closure only in patients younger than 60 years with a high risk of PFO related stroke/TIA. It is still unclear the benefit of percutaneous PFO closure in patients aged ≥60 years, except for a few patients who were included in the DEFENSE-PFO trial [52]. Subgroup analysis of the DEFENCE-PFO study suggests that PFO closure may be effective in preventing recurrent stroke in patients aged ≥ 60 years [53]. The ongoing COACH-ELDERLY ESUS trial (NCT05238610) aims to further evaluate the clinical effectiveness of PFO closure in patients over 60 years of age. More studies and evidence are needed for the association of PFO with stroke in older patients as well as an appropriate diagnostic modality for screening in these patients, which will be the basis for further clinical research regarding the treatment of this age group. Our study has some limitations. We may have had a slightly higher prevalence of cryptogenic stroke in our study, especially in patients aged ≥ 60 years as a result of patients not being followed up long enough to detect paroxysmal AF. Also, patients in the age group of ≥60 years did not undergo transesophageal echocardiography because the benefit for possible percutaneous closure of the PFO is not yet clear. In our study, atrial septal aneurysm was diagnosed based on transthoracic echocardiographic findings, whereas in other studies it is done with transesophageal echocardiography. Nevertheless, our research is still relevant. We compared the same number of patients in both age groups in a certain period of time and we included patients with moderate and mild stroke who were hospitalized or underwent outpatient treatment in our hospital. In order to have more reliable results, patients with clinically significant R-to-L shunt (grade of ≥3) that could be the cause of stroke were included in our study. In conclusion, Bubble- cTCD should be the first diagnostic modality for diagnosing PFO in elderly patients. The association of PFO with cryptogenic stroke in otherwise healthy elderly patients and the possibility of changing the strategy for further treatment should be considered.

No potential conflict of interest relevant to this article was reported.

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Резиме

ДЕСНО-ЛЕВ ШАНТ И КРИПТОГЕН МОЗОЧЕН УДАР КАЈ ПАЦИЕНТИ НАД 60 ГОДИНИ

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Цел: Да се одреди можната улога на патент форамен овале (ПФО) преку детекција на десно-лев шант кај пациентите со криптоген мозочен удар на возраст од ≥ 60 години и да се спореди преваленцијата на ПФО со мозочен удар од позната причина.

Метод: Проспективно ја испитавме преваленцијата на ПФО користејќи колор транскранијална доплер ултрасонографија со контраст (Bubble–cTCD) кај 86 последователни пациенти на возраст од ≥ 60 години со транзиторна исхемична атака (ТИА) или мозочен удар и 86 пациенти на возраст < 60 години со ТИА/мозочен удар како контролна група. Направена беше споредба на пациентите со криптоген и со мозочен удар со позната причина.

Резултати: Значително повисока преваленција на PFO кај пациентите со криптоген во споредба со пациентите со мозочен удар од позната причина е регистрирана кај пациентите на возраст < 60 години (56,6 % наспроти 18,8 %) и кај пациентите на возраст од ≥ 60 години (37,14 % наспроти 11,76 %), соодветно. Мултиваријантната анализа приспособена за возраста, хипертензијата и коронарната болест покажа дека постоењето на Д-Л шант е независно поврзано со криптогениот мозочен удар во помладата возрасна група (odds ratio, 4,012; 95 % CI1,323 до 12,171 , p = 0,0143,70) и во постарата група (odds ratio, 3,197; 95 % CI 1,140 до 10,877, p = 0,037).

Заклучок: Нашите наоди сугерираат дека ПФО е силно асоциран со криптогениот мозочен удар кај пациентите на возраст од ≥ 60 години. Bubble - cTCD беше изводлив и соодветен како почетен скрининг метод за детекција на ПФО кај постарите пациенти.

Клучни зборови: патент форамен овале; киптоген мозочен удар; транскранијален доплер ултрасонографија