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Relation Between Patent Foramen Ovale and Cryptogenic Stroke: Single-center Echocardiographic Study

Patent Foramen Ovale ve Kriptojenik İnme Arasında İlişki: Tek Merkezli Ekokardiyografik Çalışma

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Abstract

Objective: The transcatheter closure of patent foramen ovale (PFO) has been proven effective in preventing cryptogenic stroke (CS), and it is necessary to determine the structure of PFO associated with CS. In this study, we sought to evaluate the characteristics of PFO by using transesophageal echocardiography (TEE) and contrast transesophageal echocardiography (c-TEE) to assess the characteristics of PFO associated with CS and seek out the high-risk factors for PFO for CS.

Method: A total of 52 test patients who suffered CS combined with PFO and 64 control patients diagnosed with PFO without stroke were enrolled. The structure of the PFO was observed by TEE and c-TEE. The differences in PFO structure between the test patients and controls were compared.

Results: The patients in the test group were older than the controls. The height and length of the PFO during Valsalva were found to be greater in the test group than in the control group. The occurrence rates of low-angle PFO (angle between inferior vena cava and PFO ≤10°) and atrial septal aneurysm (ASA) were higher in the test group than in the control group. Right-to-left shunt (RLS) ≥ grade II during Valsalva was significantly higher in the test group than in the control group. Regarding RLS ≤ grade II during Valsalva and all grades of RLS at rest, there was no difference between the two groups. Multivariate analysis showed that the length of the PFO during Valsalva, the presence of ASA, large (≥ grade II) RLS shunt during Valsalva and low-angle PFO were independent relevant factors for CS.

Conclusion: The length of the PFO tunnel, low-angle PFO, RLS III during Valsalva and the presence of ASA were associated with a greater risk for CS. TEE combined with c-TEE may be helpful in identifying PFO patients at great risk of CS and screening for transcatheter closure of PFO.

Keywords: Cryptogenic stroke, echocardiography, patent formane ovale

Öz

Amaç: Patent foramen ovalenin (PFO) transkateter kapatılması kriptojenik inmeli (Kİ) hastalarda sıklıkla gerçekleştirilir, ancak inme ile ilişkili PFO'nun ekokardiyografik belirleyicileri bilinmemektedir. Bu çalışmada, Kİ ile ilişkili PFO'nun özelliklerini değerlendirmek ve Kİ için PFO için yüksek risk faktörlerini araştırmak üzere transözofageal ekokardiyografi (TEE) ve kontrast transözofageal ekokardiyografi (c-TEE) kullanarak PFO'nun özelliklerini değerlendirmeyi amaçladık.

Yöntem: PFO ile birlikte CS geçiren toplam 52 test hastası ve inme olmadan PFO tanısı alan 64 kontrol hastası kaydedildi. PFO'nun yapısı TEE ve c-TEE ile gözlemlendi. Test hastaları ve kontroller arasındaki PFO yapısındaki farklılıklar karşılaştırıldı.

Bulgular: Kİ geçiren hastalar kontrol grubundaki hastalardan daha yaşlıydı. Valsalva manevrası sırasında PFO'nun hem yüksekliği hem de uzunluğu Kİ grubunda kontrol grubuna göre daha fazlaydı. Düşük açılı PFO (alt vena kava ile PFO arasındaki açı ≤10°) ve atriyal septal anevrizma (ASA) görülme sıklığı Kİ grubunda kontrol grubuna göre daha yüksekti. Valsalva manevrası sırasında sağdan sola şant (RLS) ≥ derece II, Kİ grubunda kontrol grubuna göre anlamlı olarak daha yüksekti. İstirahatte RLS dereceleri açısından iki grup arasında anlamlı fark yoktu. Çok değişkenli analiz sonucunda Valsalva sırasında PFO uzunluğunun ≥10 mm olması, düşük açılı PFO, ASA varlığı ve Valsalva sırasında ≥ derece II HBS'nin Kİ'nin bağımsız öngördürücüleri olduğu belirlendi.

Sonuç: Çalışmamız TEE ve c-TEE ile belirlenen PFO'nun yapısal özelliklerinin Kİ açısından yüksek riskli hastaların belirlenmesine yardımcı olabileceğini düşündürmektedir.

Anahtar kelimeler: Ekokardiyografi, kriptojenik inme, patent foramen ovale

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Introduction

The prevalence of patent foramen ovale (PFO) in the general population is approximately 25% (1). The connection of PFO with various conditions such as cryptogenic stroke (CS) and migraine has been demonstrated (2-7). The effectiveness of transcatheter closure of PFO in preventing CS has been demonstrated, but there is limited data on the comprehensive evaluation of PFO morphology associated with the development of CS. Therefore, it is necessary to determine the structure of PFO associated with CS (8-10). Transesophageal echocardiography (TEE) allows detailed visualization of the foramen ovale area. In this study, we sought to evaluate the characteristics of PFO by using TEE and contrast transesophageal echocardiography (c-TEE) to assess the characteristics of PFO associated with CS and seek out the high-risk factors for PFO for CS.

Materials and Methods

We retrospectively recorded 116 patients diagnosed with PFO using TEE and c-TEE in the echocardiography laboratory from May 2016 to December 2023. The occurrence of cerebral infarction in patients with CS has been demonstrated using magnetic resonance imaging. CS was diagnosed by a neurologist based on the exclusion of all other identifiable causes of stroke such as large artery atherosclerosis, cardioembolism, small vessel disease, or arterial dissection after clinical examinations including brain and carotid imaging, electrocardiography, and echocardiography.

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (1964) and the study protocol was approved by Local Ethics Committee (İstanbul Atlas University Non-Invasive Research Ethics Committee: 08.01.2024, No: 01/14).

TEE

After undergoing routine transthoracic echocardiography, all patients underwent biplane TEE with saline contrast injection. The presence of PFO was confirmed by the passage of microbubbles from the right atrium to the left atrium within the three cardiac cycles following opacification of the right atrium using intravenous agitated saline contrast injection. The anatomical and functional characteristics of PFO, including PFO height, tunnel length, presence of atrial septal aneurysm (ASA), hypermobile interatrial septum, presence of prominent Eustachian valve or Chiari's network, grade of right-to-left (RL) shunt at rest and during the Valsalva maneuver, and the angle between the inferior vena cava (IVC) and PFO, were assessed by independent cardiologists who were unaware of the patient's CS status. The height of the PFO was measured as the maximum separation between the septum primum and septum secundum in the end-systolic frame, and a height greater than 2 mm was classified as indicative of a large-sized PFO (11). The length of PFO tunnel was determined by measuring the maximum overlap between the septum primum and septum secundum, and a length greater than 10 mm was designated as indicative of a long-tunnel PFO (12). ASA was characterized by a septal excursion of greater than 10 mm from the midline into the right or left atrium, or a total excursion of more than 15 mm between the right and left atrium (2). Additionally, we defined a hypermobile interatrial septum as a moving and floppy septum with a septal excursion exceeding 5 mm in every heartbeat. The grade of RL shunt was assessed at rest and during Valsalva maneuver using agitated saline contrast. The maximum number of microbubbles that appeared in the left atrium was counted in a single frame, and the large (≥ grade II) RLS shunt was defined as >20 microbubbles (2,9). We measured the angle between the IVC and the PFO flap on an imaging plane that displayed the IVC and interatrial septum. An angle of the PFO from the IVC less than 10 degrees was defined as indicative of a low-angle PFO.

Statistical Analysis

The data are expressed as mean ± standard deviation for continuous variables and as numbers and percentages for categorical variables. Differences between the two groups were analyzed using the t-test and Mann-Whitney U test for continuous variables, and the chi-square test for categorical variables. Univariate and multivariate logistic regression analyses were conducted to identify independent factors associated with CS. All p-values were 2 sided, and a $p<0.05$ was considered statistically significant. All statistical assessments were carried out using the Statistical package for Social Sciences (SPSS for Windows, version 23.0. IBM Corp. Armonk, NY, USA) software.

Results

A total of 52 test patients who suffered CS combined with PFO and 64 control patients diagnosed with PFO without stroke were enrolled. The mean age of all patients was 41±17 years. The comparison of patient characteristics between those with CS and those without CS is presented in Table 1.

Patients with CS were older than those without CS (48±15 vs. 40±18, p=0.01). The prevalence of hypertension (36% vs. 14%, p=0.02) and smoking (38% vs. 17%, p=0.03) was higher in patients with CS compared to those without CS.

Comparisons of the echocardiographic characteristics of PFO between the two groups are shown in Table 2. The height (2.4±1.7 vs. 1.6±1.1, p<0.01) and length (9.3±4.5 vs. 8.1±4.3, p=0.03) of the PFO during Valsalva were found to be greater in the test group than in the control group. The occurrence rates of low-angle PFO (angle between IVC and PFO ≤10°) (27% vs. 8%, p<0.01) and ASA (39% vs. 11%, p<0.01) were higher in the test group than in the control group. The large (≥ grade II) RLS shunt during Valsalva was significantly higher in the test group than in the control group (25% vs. 8%, p<0.01). Regarding RLS ≤ grade II during Valsalva and all grades of RLS at rest, there was no difference between the two groups. Multivariate analysis showed that the length of the PFO during Valsalva [odds ratio (OR)= 3.27, p=0.03], the presence of ASA (OR= 4.96, p=0.02) large (≥ grade II) RLS shunt during Valsalva (OR= 3.63, p=0.02) and low-angle PFO (OR= 5.80, p=0.01) were independent relevant factors for CS.

Table 1. Patient characteristics

	CS group (n=52)	Control group (n=64)	p-value
Age, years	48±15	40±18	0.01
Woman	28 (54)	30 (47)	>0.05
Hypertension	19 (36)	9 (14)	0.02
Diabetes mellitus	3 (5)	2 (3)	>0.05
Smoking	20 (38)	11 (17)	0.03

Data are presented as mean ± standard deviation or number (%) of patients. CS: Cryptogenic stroke, chi-square test, t-test and Mann-Whitney U tests were used, as apropiate

Discussion

A PFO is a highly prevalent finding in cryptogenic ischaemic stroke, particularly in young adults. A common challenge in clinical practice is to distinguish between incidental and pathogenic PFO. Some clinical features and tools such as the risk of paradoxical embolism score may help determining the probability of a stroke-related PFO. Nonetheless, the best therapeutic option to reduce stroke recurrence after a CS with PFO has been a matter of debate for a long time.

The current study assessed the anatomical and functional characteristics of PFO in patients with CS and those without CS. Long-tunnel PFO, the presence of hypermobile interatrial septum, the large RL shunt during Valsalva maneuver, and low-angle PFO were identified as independent factors associated with CS.

A hypermobile interatrial septum, characterized by a floppy septum with movement of the free edge in every

Table 2. Echocardiographic characteristics of PFO

	CS group (n=52)	Control group CS (n=64)	p-value
Length of PFO, mm	9.3±4.5	8.1±4.3	0.03
Height of PFO, mm	2.4±1.7	1.6±1.1	<0.01
Long-tunnel PFO (>10 mm)	28 (54)	18 (28)	<0.01
Large-size PFO (>2 mm)	11 (21)	4 (6)	<0.01
Hypermobile interatrial septum	38 (73)	9 (14)	<0.01
Atrial septal aneurysm (ASA)	20 (39)	7 (11)	<0.01
Angle between IVC and PFO, degrees	27±18	36±17	<0.01
Low-angle PFO (<10°)	14 (27)	5 (8)	<0.01
≥ Grade II RLS	13 (25)	5 (8)	<0.01

Data are presented as mean ± standard deviation or number (%) of patients. CS: Cryptogenic stroke, PFO: Patent foramen ovale, RLS: Right-to-left, chi-square test, t-test and Mann-Whitney U tests were used, as apropiate

Table 3. Independent predictors of cryptogenic stroke according to the multivariate regression analyses in the study population

	Odds ratio (95% CI)	p-value
Long-tunnel PFO (>10 mm)	3.27 (1.11-10.6)	0.03
Atrial septal aneurysm (ASA)	4.96 (1.82-13.5)	0.02
Low-angle PFO (<10°)	5.80 (1.38-29.7)	0.01
Moderate to large (≥ grade II) RLS shunt during valsalva maneuver	3.63 (1.23-11.3)	0.02

PFO: Patent foramen ovale, RLS Right-to-left, CI: Confidence interval. Logistic regression analyses stepwise forward was used

heartbeat, can frequently result in the enlargement of the PFO orifice, thereby increasing the potential for thrombus passage (2). In our study, we found that the presence of hypermobile interatrial septum was associated with CS. Our findings indicate that the presence of a hypermobile interatrial septum and ASA should be meticulously assessed using TEE. The mechanism of CS may be connected to the angle between the IVC and PFO. Our study presents fresh evidence indicating a correlation between CS and a low angle between the IVC and PFO. This low angle may selectively guide blood flow from the IVC toward the interatrial septum and the orifice of the PFO.

Consistent with the prior investigation (12,13), our study demonstrates an association between CS and a PFO with an extended tunnel length. The extended tunnel length of PFO could potentially serve as a location for thrombus formation due to turbulent and stagnant blood flow, as indicated in previous research (12).

New randomized trials have provided evidence supporting the effectiveness of transcatheter closure in reducing the occurrence of strokes when compared to traditional medical therapy (8-10). The length of the PFO tunnel, low-angle PFO, large (≥ grade II) RLS shunt during Valsalva and the presence of ASA were associated with a greater risk for CS. TEE combined with c-TEE may be helpful in identifying PFO patients at great risk of CS and screening for transcatheter closure of PFO.

Study Limitations

Our study contains some limitations. In our study, CS was diagnosed by a neurologist based on the exclusion of all other identifiable causes of stroke such as large artery atherosclerosis, cardioembolism, small vessel disease, or arterial dissection after clinical examinations including brain and carotid imaging, electrocardiography, and echocardiography. Apart from these basic investigations, a detailed thrombophilia panel could not be checked in every patient. Additionally, asymptomatic paroxysmal atrial fibrillation attacks could not be examined in detail in every patient. Another limitation is that brain MRI findings and localizations were not recorded in CS patients.

Conclusion

A higher risk for CS was linked to the length of the PFO tunnel, low-angle PFO, substantial (≥ grade II) RLS shunt during Valsalva, and the presence of ASA. When screening for transcatheter closure of PFO and dentifying PFO patients at high risk of CS, TEE in conjunction with c-TEE may be useful.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (1964) and the study protocol was approved by Local Ethics Committee (İstanbul Atlas University Non-Invasive Research Ethics Committee: 08.01.2024, No: 01/14).

Informed Consent: Not necessary for this manuscript.

Authorship Contributions

Concept: Z.D., G.B., Design: Z.D., Data Collection or Processing: Z.D., G.B., Analysis or Interpretation: G.B., Literature Search: Z.D., Writing: Z.D., G.B.

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