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47
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Patent Foramen Ovale: A Practical and Imaging Based Morphological Classification

Begüm Yetiş Sayın, Ali Oto

Ankara Memorial Hospital, Clinic of Cardiology, Ankara, Turkey

Abstract

Objectives: Patent foramen ovale (PFO) has been implicated in cryptogenic stroke, transient ischemic attacks, migraine with auras, decompression sickness and severe refractory hypoxemia. Recently published data provided sufficient evidence for the percutaneous closure of PFO in the embolic stroke of an undetermined source. After a suspicion for a paradoxical cerebral embolism, a transthoracic echocardiography, transcranial doppler study, and transesophageal echocardiography using contrast bubble injection are indicated. Detection of PFO is possible during contrast bubble injection with or without Valsalva maneuver in transesophageal echocardiography. Three- or two-dimensional transesophageal echocardiography (TEE) give opportunity to obtain detailed information about complex anatomical variations in PFO morphologies including atrial septal aneurysm, large tunnel, increased height of PFO, lipomatous hypertrophy. Ideal device selection is important for the appropriate closure of PFO. A standardized classification is needed to define PFO morphologies when selecting the device size. In our study, we aimed to create a common language for different and high-risk morphologies with two-dimensional (2D) and three-dimensional (3D) TEE in patients with cryptogenic stroke that would be helpful in transcatheter PFO closure.

Materials and Methods: One hundred eleven one patients with the diagnosis of cryptogenic stroke and with high "The Risk of Paradoxical Embolism" (RoPE) score (>7) were included in the study. From the recorded images, interatrial septum was evaluated retrospectively with 2D and 3D TEE. Also, transcranial doppler, contrast bubble injection in TEE, 12-lead electrocardiography was performed. The amount of shunting during bubble study was recorded. According to analysis with 2D and 3D TEE technique, we classified the subtypes of different PFO morphologies into two main types and subgroups according to atrial septal aneurysm.

Address for Correspondence: Begüm Yetiş Sayın, Ankara Memorial Hospital, Clinic of Cardiology, Ankara, Turkey
e-mail: begumyts@yahoo.com **ORCID:** orcid.org/0000-0001-9605-8829
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Abstract

Results: 2D and 3D transesophageal echocardiography was applied to all patients before and during the PFO closure procedure. The amount of shunting was severe in 64 patients (57.7%) patients. PFO tunnel was found to be spontaneously open in 64 patients. Most of patients had long PFO tunnel and mean tunnel length was 11.47±2.26 mm. The mean atrial septal defect (ASD) size accompanying PFO was 3.17±1.64 mm (large ASD). There were atrial septal defects accompanying PFO in 28 (25.2 %) patients. The mean of opening length of PFO (height of PFO) which can induce severe shunting was 4.06±1.6 mm. Atrial septal aneurysm was existed in 22 (19.8 %) patients. The total amount of other then simple morphologies which carry high risk features were higher. We found that the most frequent device selected by the operator was multi-fenestrated septal occluder (cribriform). The multi-fenestrated septal occluder devices were implanted in 69.4% of patients. The more complex anatomy led the operator for to choose mostly multi-fenestrated devices.

Conclusion: After defining PFO morphologies and categorizing the different types, we would be able to express the same morphological classification which could be easily and repetitively used. With the usage of a well-known classification, device type selection could be standardized for optimization of percutaneous transcatheter closure of PFO while minimizing the complications and increasing procedural success.

Keywords: Patent foramen ovale, cryptogenic stroke, percutaneous closure of patent foramen ovale

Introduction

Patent foramen ovale (PFO) is one of the anatomical variants of the interatrial septum and considered to be a subclass of ostium secundum defects. Blood flow through the foramen ovale permits the passage of oxygenated blood from the right atrium into the left atrium in fetal circulation. Two membranes, septum secundum and septum primum, are part of the interatrial septum and fuse soon after birth with the increase in left atrial pressure. However, in 15-35% of patients this fusion does not occur and may serve as a conduit for paradoxical embolization. The flap valve of PFO allows only a right-to-left shunt, either when the right atrial pressure exceeds the left atrial pressure during a short interval of cardiac cycle or following a straining maneuver (Valsalva Maneuver). The size and morphology show a great variability among patients. Associated defects such as atrial septal aneurysm (ASA), atrial septal defects (ASD) make the morphology of the interatrial septum more complicated[1]. Although mostly encountered as innocent, PFO has been reported to be associated with cryptogenic stroke, migraine, peripheral embolism, platypnea-orthodexia syndrome and Alzheimer's dementia[2]. A cryptogenic stroke is defined as an ischemic stroke with an unknown cause which constitutes one-third of all stroke patients. Association between cryptogenic stroke and the presence of PFO causing paradoxical emboli have been demonstrated in several studies[3]. Young population are mostly affected by PFO-related embolic events. PFO is found to be the cause in 40-56% of stroke patients under the age of 55. However, it is still controversial whether PFO is an incidental finding in some of the cryptogenic stroke patients. Percutaneous PFO closure and antithrombotic therapy are available options for secondary prevention in PFO-related strokes[3,4]. Many studies and metanalyses tried to demonstrate that a device-closure strategy could be superior to a medical-therapy strategy. Hypermobile atrial septum, channel length or height of PFO, presence of ASA or degree of shunt from PFO that are identified in transesophageal echocardiography (TEE) may contribute to the ischemic cerebrovascular events. The Risk of Paradoxical Embolism (RoPE) score calculator is used to define stroke risk estimation in PFO patients for decision of PFO closure. A new risk estimation system with the use of PFO features (ASA or long tunnel length) and ROPE score simultaneously was also defined in a recent study[5,6].

Different morphologic features of PFO may predispose to cerebrovascular events and frequently associated with cryptogenic stroke[7-9]. Morphologic definitions and classifications of PFO are based on limited autopsy studies and may not be applicable to the clinical practice[10,11]. Two-dimensional (2D) or three-dimensional (3D) TEE provides accurate imaging of the interatrial septum and help defining the detailed morphology of the PFO which could be high risk for cerebrovascular events. On the other hand, anatomical variations seen in patients undergoing transcatheter device closure may influence device selection and procedural success. Inappropriate closure procedure could be a result of a complex anatomical feature. 2D TEE with agitated saline contrast is currently gold standard for diagnosis of PFO[1,9]. 3D TEE allows direct visualization of the entire fossa ovalis with surrounding structures and also bubbles crossing fossa ovalis. A standardized definition and classification of PFO morphology including accompanying structures is needed for the decision of percutaneous PFO closure procedure, device selection or sizing in PFO closure procedures. An ideal device selection is important to facilitate apposition and fusion of the septum primum and septum secundum.

We aimed to propose a practical new classification of different morphologies with 2D and 3D TEE in patients with cryptogenic stroke to create a common language when defining a high risk PFO type based on the data of our series. We believe such classification will be helpful in practice of PFO closure and fill a gap.

Materials and Methods

One hundred eleven one patients who were referred to cardiology department and evaluated by TEE between 2014 and 2020 with the diagnosis of cryptogenic stroke and with high RoPE score (≥7) were included in this study. All patients were confirmed for embolic ischemic stroke with magnetic resonance imaging (MRI). MRI of the brain with three sequences (T2 sequence, diffusion-weighted imaging, and fluid-attenuated inversion recovery) was used to diagnose acute stroke. Patients with carotid artery stenosis, uncontrolled diabetes or hypertension, a high-risk source of cardioembolism such as atrial fibrillation or major structural cardiac anomaly and prothrombotic disorder were excluded. Before evaluating the defect in interatrial septum by 2D and 3D TEE, extensive workup consisting of transcranial doppler, echocardiography, 12-lead electrocardiography was performed. Also, with bubble study, the amount of shunting across the PFO was evaluated during transcranial doppler and echocardiography.

Recorded images with the General Electric Vivid E9 (GE Health Medical, Horten, Norway) were used. The 2D and 3D TEE images were evaluated retrospectively. Definition and characterization of PFO morphologies were classified according to the additional defects detected with PFO, spontaneous opening of PFO tunnel (spontaneous or provokable right-to-left shunt), PFO size (maximum separation between septum primum and septum secundum overlap at the point of entry into the left atrium), presence of interatrial septal aneurysm, thickness of primum and secundum septum (lipomatous hypertrophy), passage of agitated saline from PFO tunnel with Valsalva or spontaneously. The length of tunnel was noted. The degree of right-to-left shunting, at rest and during the Valsalva maneuver, was defined as mild when 3 to 9 microbubbles appeared, moderate if 10 to 30 microbubbles appeared, and severe if >30 microbubbles appeared. Bubbles appearing in the left atrium (shunt occurring) within the third cardiac cycle was taken as a cut off time. All saline injections were performed from antecubital vein[8]. Atrial septal aneurysm was diagnosed as 15-mm of total septal tissue excursion or a 10-mm protrusion into either atrium from the septal midline[11,12]. According to analysis with 2D and 3D TEE technique, we classified the subtypes of different PFO morphologies causing cryptogenic stroke as follows:

Type I- A tunnel morphology without ASD or ASA

a. Closed PFO tunnel opened and passage of agitated saline with Valsalva maneuver (Figure 1)

b. A spontaneously opened PFO tunnel, passage of bubbles without Valsalva maneuver (Figure 2)

Type II- More complicated morphology with ASD, ASA or lipomatous hypertrophy

a. PFO tunnel with small ASD next to the tunnel (Figure 3)

b. PFO tunnel with multiple defects or a large ASD (defined as greater than 3 mm) (Figure 4a,b)

c. PFO with atrial septal aneurysm and increase in PFO size with Valsalva maneuver (Figure 5a,b)

d. PFO with atrial septal aneurysm with increase in PFO size with Valsalva maneuver and ASD (Figure 6)

e. PFO with atrial septal aneurysm and/or lipomatous hypertrophy (Figure 7a,b)

Percutaneous PFO closure procedures were performed to all patients included in the study. The devices were implanted under fluoroscopic and 2D/3D TEE echocardiographic guidance according to standard technique while the patient was under general anesthesia. The type of device was chosen with decisions of interventional cardiologist and echocardiographer according to morphologies.

Statistical Analysis

Data analyses and statistical analyses were performed by using SPSS 23 for Windows (SPSS Inc., Armonk, NY, USA). Distribution of data was assessed by using Shapiro-Wilk test or Kolmogorov-Smirnov test. Numerical variables were presented as mean ± standard deviation or median (quartile deviation), and categorical variables were presented as percentages.

Results

One hundred eleven one patients (age ranged between: 18-68 years, 36.9% male and 63.1% female) who had a cerebrovascular event were evaluated. 2D and 3D transesophageal echocardiography was applied to all patients before and during the PFO closure procedure. All patients had been evaluated with magnetic resonance imaging showing different number and location of ischemic lesions. After shared decision making and consultation with neurology, PFO closure was decided in patients who had ischemic lesions in MRI. All patients had high RoPe score (RoPE ≥7) Passage of intravenously injected microbubbles in transcranial doppler with different types of severity was demonstrated in all patients. During TEE imaging, mild shunt was demonstrated in two patients (1.8%) and moderate shunt was in 45 patients (40.5%). The amount of shunt after saline injection in TEE was severe 64 (57.7%) patients. The baseline demographic and clinical characteristics of patients were summarized in Table 1.

There were atrial septal defects accompanying PFO in 28 (25.2%) patients. The mean ASD size accompanying PFO was 3.17±1.64 mm. Mean tunnel length was 11.47±2.26 mm. A simple PFO tunnel was found to be open spontaneously in 26 (49.4 %) patients. Opening length of PFO (height of PFO) which can induce severe shunting was 4.06±1.6 mm. Lipomatous hypertrophy was detected in five (4.5%) patients and atrial septal aneurysm was existed in 22 (19.8%) patients. PFO tunnel was found to be spontaneously open in 64 patients. The distribution of different morphologies according to new classification is shown in Figure 8.

The total amount of other morphologies which carry high risk features other than Type Ia were higher.

Table 1. Baseline demographic and clinical characteristics of patients

Demographic and clinical characteristics	Patients (n=111)
Age (years)	18-68
Gender (%) Male Female	 36.9% 63.1%
RoPE score	≥7
Severe shunt from PFO tunnel (%)	57.7%
Spontaneous right-to-left shunting from PFO (%)	57.6%
PFO with ASD (%)	25.2%
PFO with ASA (%)	19.8%
Mean tunnel length (mm)	11.47±2.26
Mean ASD size (mm)	3.17±1.64
Mean PFO height (mm)	4.06±1.6

RoPE: The risk of paradoxical embolism, ASD: Atrial septal defect, ASA: Atrial septal aneurysm, PFO: Patent foramen ovale, n: Number

All patients were evaluated with TEE imaging during percutaneous PFO closure. The device types and size of the selected devices were evaluated. We found that the most frequent device diameter selected by the operator was multi-fenestrated septal occluder (cribriform) (9-ASD-MF-025) Amplatzer Multi-Fenestrated Septal Occluder. The second most used device was Amplatzer 9-PFO-025. Other devices which were selected are shown in Figure 9.

The multi-fenestrated septal occluder devices were implanted in 69.4% of patients. All devices were successfully implanted and there were no complications after device implantation.

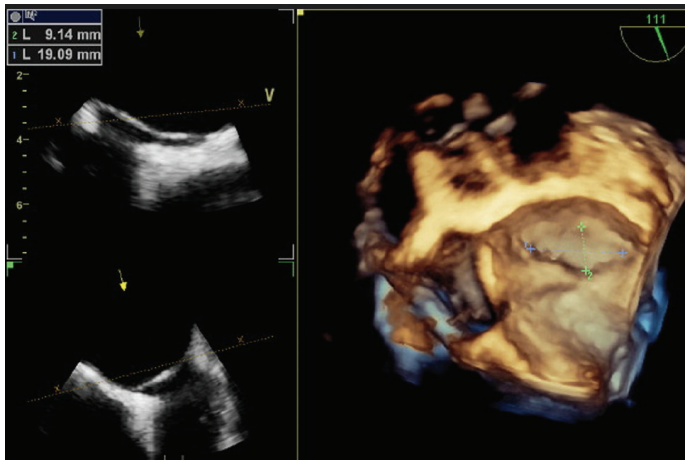

Figure 1. Type Ia

Discussion

In this study we analyzed the structural differences in PFO morphology with TEE and we propose a standardized definition for the additional defects. Although mostly left undetected due to its asymptomatic nature, PFO can potentially lead to paradoxical embolism with either transient or continuous right-to-left shunt. Three randomized clinical trials and meta-analyses of all the available studies showed that in selected patients with cryptogenic stroke, PFO closure is superior to medical therapy for the secondary prevention of stroke[13-15]. Appropriate patient selection should be carried out by a team composed of cardiologists and stroke neurologists. Retrospective analysis from recent studies developed a model for risk estimation which is a Risk of Paradoxical Embolism (RoPE) score. A high RoPE score identify patients with PFO-mediated cryptogenic stroke (CS). However, this score is limited in determining risk of anatomical features. Two categories for anatomical characteristics of PFO were defined as simple and complex including amount of shunt, multiple openings, length and thickness of tunnel. Some anatomical features may prevent appropriate closure, increase the risk of complications and may cause incomplete PFO closure[1,5,13].

PFO should be considered as an anatomical variant. Morphologic feature of PFO had mostly been defined from the heart specimen observations. Any failure in the

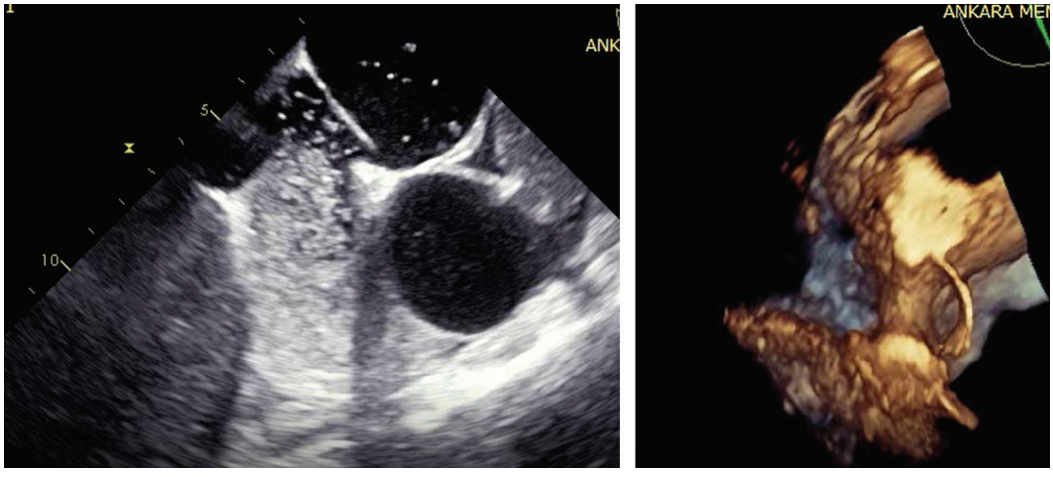

Figure 2. Type Ib

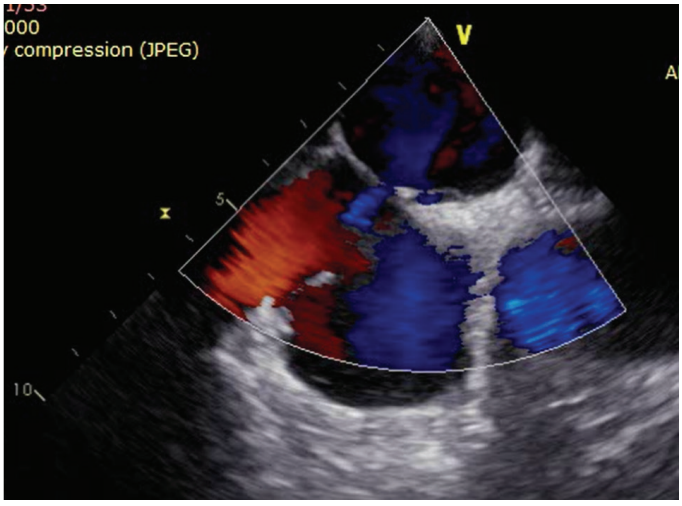

Figure 3. Type IIa. A small ASD next to the tunnel
ASD: Atrial septal defect

dynamic feature of the flap valve competence in addition to the differences in surrounding structures may affect the risk profile of PFO triggering CS[14-17]. Today TTE, TEE, intracardiac echocardiography and TCD provides detailed information about additional structures accompanying PFO. All these modalities can improve image quality with or without administration of a contrast agent. In some of the cases the distinction between ASD and PFO is not simple. Some authors suggested that large left and right atrial openings of the PFO with a short tunnel should be considered as ASD. An additional defect of ASD would cause a left to right shunt[1,18].

The majority of PFOs cannot be detected at rest and contrast bubble study during Valsalva maneuver is

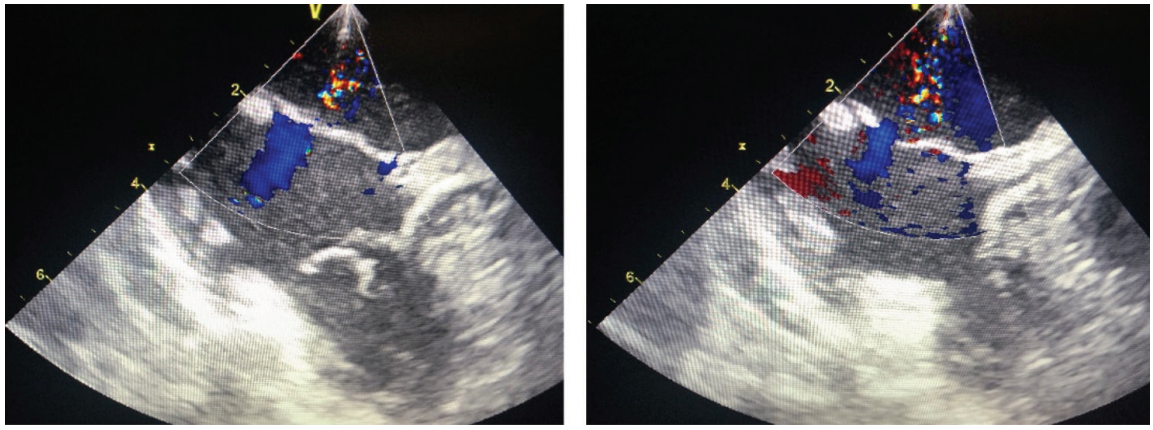

Figure 4a, b. Type IIb (multiple defects with PFO)
PFO: Patent foramen ovale

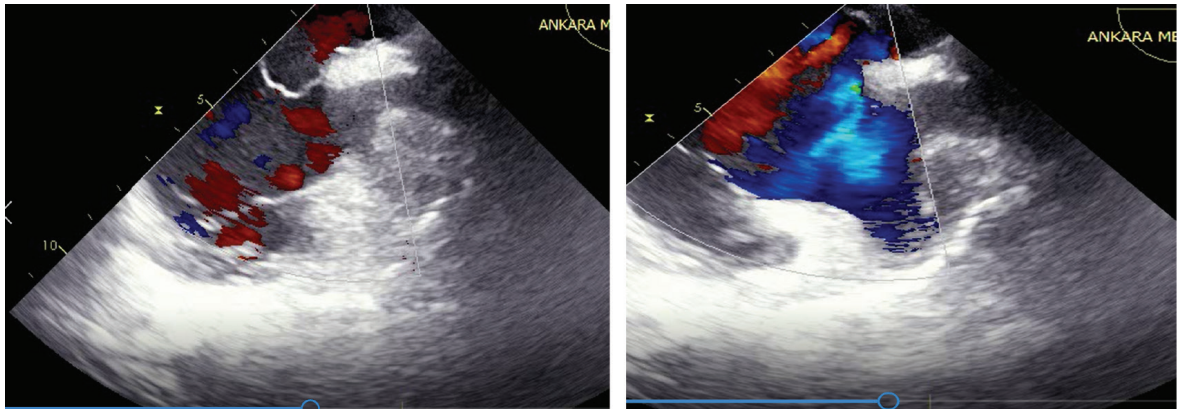

Figure 5. a) Type IIc ASA and PFO tunnel before Valsalva. **b)** ASA and increase in PFO size after Valsalva
ASA: Atrial septal aneurysm, PFO: Patent foramen ovale

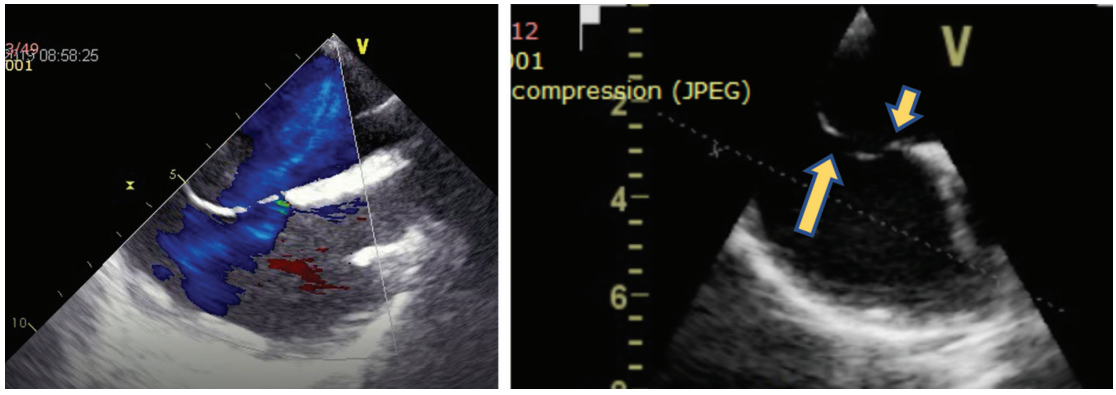

Figure 6. a) Type IId:ASA and ASD. **b)** ASD and PFO with ASA

ASD: Atrial septal defect, PFO: Patent foramen ovale, ASA: Atrial septal aneurysm

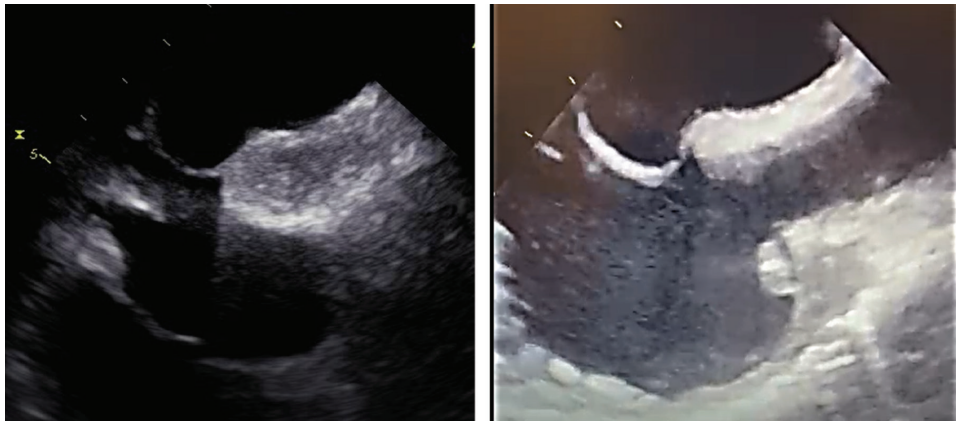

Figure 7. a) Type IIe Lipomatous hypertrophy and PFO. **b)** Type IIe ASA and PFO

PFO: Patent foramen ovale, ASA: Atrial septal aneurysm

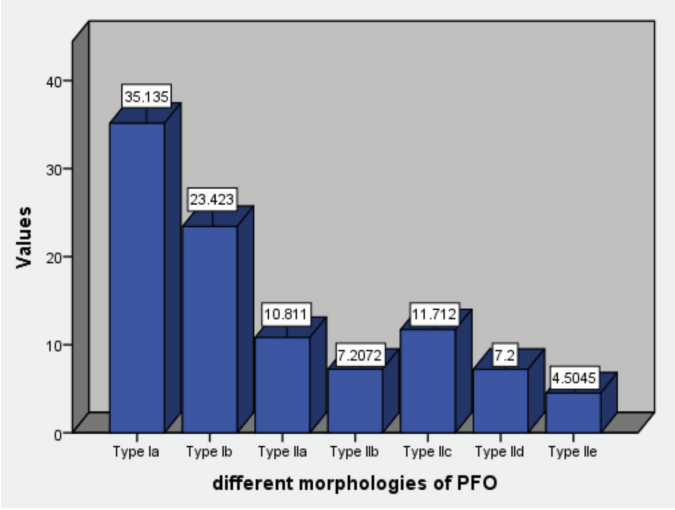

Figure 8. The distribution of different morphologies according to new classification

PFO: Patent foramen ovale

essential[19]. In our study, we performed contrast test with agitated saline bubbles in transthoracic echocardiogram which is a simple technique to suspect PFO. Following TTE, every patient had been taken to TEE and TCD. In our series Type Ia morphology, as a simple tunnel opening with Valsalva was the most common type of PFO. Presence of additional features in morphology that accompanies PFO, increases the risk of paradoxical embolism. In a study, the height of PFO tunnel, thickness of septum secundum and septal excursion distance (septal mobility), ASA was found to be greater in symptomatic patients with cryptogenic stroke or transient ischaemic attack (TIA)[20]. Moreover, the presence of ASA was found to be more important than the degree of shunting with regard to stroke recurrence[21].

A long tunnel PFO, ASA or septal excursion, large right to left shunts at rest and during Valsalva were frequently observed in patients with CS. PFO with two or more accompanying factors should be considered as high risk PFO causing higher probability for CS[19]. In our study, we found that the sum of all different morphologies was greater than simple defects (64.8%). We categorized PFO types into two main groups. ASA accompanying other PFO morphologies like ASD was used to define PFO subtypes. Patients with a long-tunnel morphology (>8-10 mm) have been found to have predisposition to clot formation[1,7,22]. In our study, the mean tunnel length was found to be 11.47±2.26 mm which pointed a high risk in paradoxical embolism. We claim that such morphological definitions made by 3D TEE and 2D TEE would provide us information about exact therapeutic indications for prevention of CS and navigate us through decision in transcatheter PFO closure.

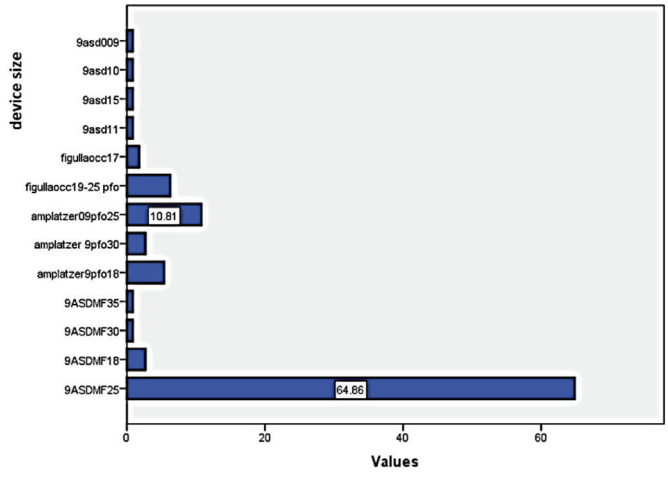

Figure 9. The type of selected devices

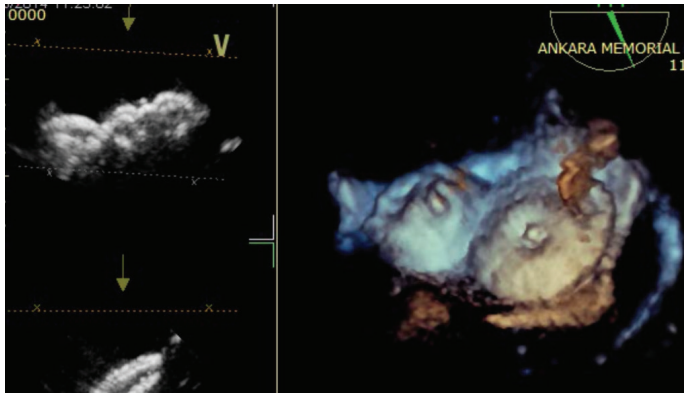

Figure 10. Closure of multiple defects accompanying PFO
PFO: Patent foramen ovale

In our series, the mean length of PFO height (PFO size) was 4.06±1.6 mm. While categorizing Type IId and Type IIe morphologies, we used PFO height (PFO size) parameter. Schuchlenz et al.[23] has found a relation between PFO size and risk for cerebrovascular events. They suggested that a PFO size (maximal separation between septum primum and secundum) greater and equal to 4 mm was associated with ischemic stroke or TIA. When taken into account ASD with PFO as a risk factor, additional defects such as small ASD near PFO tunnel or large ASD apart from PFO tunnel, which we had defined under type II defects, could be an increasing risk mimicking the risk of PFO height.

Recurrence rate of paradoxical cerebral embolism is reported to be between 3.4% and 11%. Percutaneous closure of a PFO with different types of devices are feasible in patients with presumed paradoxical embolism[24,25]. Recently, most PFO closure devices are ASD closure devices modified for PFO anatomy[26]. Selection of a device type should be made according to morphologies accompanying PFO. Sievert et al.[26] defined three distinct morphologies during a course of device closure study in order to place an "in tunnel" PFO closure system. In this categorization type1 consisted of simple tunnel anatomy, type 2 included defects with aneurysmal septum primum that maintains a stable length (a minimum of 4 mm) of tunnel that is not aneurysmal and remains stable overlapping the septum secundum. Type III had an aneurysmal septum primum that has no stable length of tunnel to allow placement of an "in-tunnel" PFO closure system. In our classification, we defined overall morphology when most of the defects included the complex anatomical variances including ASA, ASD, lipomatous hypertrophy and we have showed that multi-fenestrated devices were more successfully implanted in complicated anatomies.

We also prevented device embolization by defining the full morphology especially in the presence of ASA or ASD. Two device strategy sometimes could be applied in the presence of multiple defects accompanying PFO (Figure 10).

Study limitations

Long term follows up of our patients are needed in order to find out if the device selection would affect the prognosis of patients, recurrence of CS or complications after device implantation. In this study, every patient had cryptogenic stroke; we did not have any control group.

Conclusion

Characterization and defining types of PFO provides us using the same language for standardized shared decision making and proper patient selection in PFO closure. Considering highly variable anatomical morphology with respect to size, tunnel length, redundancy of septum, thickness of septum secundum and relationship to neighboring structures, one type of device might not be suitable for optimal treatment of PFOs. We suggest that by defining PFO morphologies and categorizing the different types, we would express the same morphological classification which could be easily and repetitively used. After this classification, the appropriate device type selection could be standardized for optimization of percutaneous transcatheter closure of PFO while minimizing the complications and increasing the procedural success. Further studies are required for decision making in PFO closure and comparison with medical therapies.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Bursa Yüksek İhtisas University Non-Interventional Clinical Research Ethics Committee on 08.04.2022 with decision number 20220504.

Informed Consent: The authors declare no conflict of interest.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yetiş Sayın B, Oto A, Concept: Yetiş Sayın B, Oto A, Design: Yetiş Sayın B, Oto A, Data Collection and/or Processing: Yetiş Sayın B, Analysis and/or Interpretation: Yetiş Sayın B, Oto A, Literature Search: Yetiş Sayın B, Oto A, Writing: Yetiş Sayın B, Oto A.

Conflict of Interest: No conflict of interest was declared by the authors.

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