

My Approach to Patent Foramen Ovale Closure

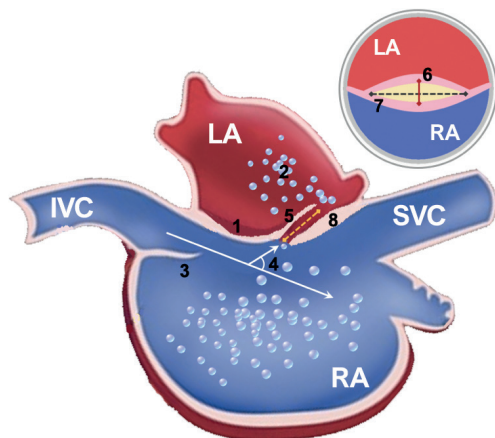
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Central Illustration: Echocardiographic Analysis for Diagnosis, Risk Stratification, and Planning of Percutaneous PFO Closure



1. Aneurysm/hypermobility of the interatrial septum
2. Magnitude of the right-to-left shunt
3. Eustachian valve
4. Angle between the IVC and the PFO tunnel
5. Tunnel length
6. Tunnel height
7. Tunnel width
8. Thickness of the septum secundum

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Schematic representation of the bicaval echocardiographic projection (lower figure on the left) and "en face" view of the PFO (upper figure on the right). IVC: inferior vena cava; LA: left atrium; PFO: patent foramen ovale; RA: right atrium; SVC: superior vena cava. White lines: angle between the IVC and the PFO tunnel. Yellow line: PFO tunnel length. Red line: PFO tunnel height. Black line: PFO tunnel width.

Abstract

The patent foramen ovale (PFO), a relatively common and generally benign finding, has been associated with paradoxical embolisms. The closure of PFO, performed in patients with cryptogenic stroke, has been shown to reduce the recurrence rates of ischemic events, as evidenced by recent clinical trials. In this article, the authors synthesize the crucial role played by echocardiography in this context, from diagnosis and risk stratification to planning and monitoring of percutaneous intervention.

Introduction

Patent foramen ovale (PFO), a remnant of fetal circulation, is prevalent in 25% of the population.¹ The

presence of PFO has often been associated with paradoxical embolism or local thrombus formation, with consequent embolic ischemic stroke.¹ However, due to the high prevalence of PFO in the population, the cause-effect correlation with ischemic stroke remains controversial.

Older randomized studies with PFO closure did not show benefits compared to antiplatelet or anticoagulation therapy in the prevalence of ischemic stroke.²⁻⁴ Recently, new studies⁵⁻⁷ and reevaluation of the RESPECT⁸ study concluded that percutaneous PFO closure is beneficial for reducing cryptogenic ischemic stroke, without increasing the risk of serious complications (Table 1). Thaler et al. identified an improvement in the characterization of ischemic stroke related to PFO using a clinical risk score, named RoPE (Risk of Paradoxical Embolism), which takes into account age; presence of risk factors such as diabetes, hypertension, and smoking; and type of image found on skull tomography (Table 2), where scores greater than 7 indicate the ischemic stroke-PFO association.⁹

Combined with the RoPE score, the high-risk anatomical characteristics of PFO must be evaluated.^{10,11} In a meta-analysis of 6 studies, the RoPE score was associated with the anatomical-clinical risk classification named PASCAL (PFO-Associated Stroke Causal Likelihood) (Table 3). The application of this classification system, proposed by Kent et al.,¹² has the potential to guide individualized decision-

Keywords

Brain Ischemia; Foramen Ovale

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Table 1 – Summary of the results of multicenter studies on percutaneous PFO closure compared to medical treatment

	Number of patients	Result	High-risk PFO (%)	Relative risk 95% CI	P	NNT/years
Closure I (2012) ²	909	Negative	42.7	1.48 (0.36 to 6.14)	0.53	----
PC (2013) ³	414	Negative	37.2	0.59 (0.06 to 6.15)	0.558	----
RESPECT (2017) ⁸	980	Positive	63.2	0.29 (0.13 to 0.69)	0.002	43/5
REDUCE (2017) ⁶	664	Positive	41.1	0.08 (0.01 to 0.52)	<0.001	33/3
CLOSE (2017) ⁵	653	Positive	100	0.05 (0.00 to 0.88)	0.002	20/5.3
DEFENSE PFO (2018) ⁷	120	Positive	100	0.07 (0.00 to 0.26)	0.13	10/2.1

Closure I: Evaluation of the STARFlex Septal Closure System in Patients With a Stroke and/or Transient Ischemic Attack to Presumed Paradoxical Embolism Through a Patent Foramen Ovale; PC: Clinical Trial Comparing Percutaneous Closure of PFO Using the Amplatzer PFO Occluder With Medical Treatment in Patients With Cryptogenic Embolism; RESPECT: Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Establish Current Standard of Care Treatment; REDUCE: PFO closure with the Gore Septal Occluder ; CLOSE, Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; DEFENSE-PFO, Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients with High-Risk Patent Foramen Ovale. CI: confidence interval; NNT: number needed to treat; PFO: patent foramen ovale. Adapted from Song, 2023.¹⁵

making. Despite these relevant clinical and structural data, which make it possible to expand percutaneous treatment, the indication for PFO closure according to the neurology guidelines¹³ is restricted to patients with proven embolic ischemic stroke, between 18 and 60 years of age, with high-risk anatomical and functional characteristics. More recently, the Society for Cardiovascular Angiography and Interventions guidelines¹⁴ expanded the recommendation of PFO closure to proven hypoxemia in platypnea-orthodeoxia syndrome, patients with systemic embolism and PFO without another cause, and patients over 60 years of age with proven embolic ischemic stroke without other causes. However, these last recommendations have a low level of evidence.

Echocardiography is fundamental for diagnosis, risk stratification, and monitoring of PFO closure. The anatomical characteristics of PFO will be described, with the main criteria for high anatomical risk and recommendations for adequate monitoring of percutaneous closure.

Diagnosis

Transthoracic echocardiography

Diagnosis of PFO by transthoracic echocardiography must be carried out while injecting agitated saline solution and performing the Valsalva maneuver. Color Doppler alone, even at low speeds, has low sensitivity because pressure equalization may occur between the atria with the absence of shunt at the time of the examination. Blood flow through the inferior vena cava favors the passage of macrobubbles through the PFO. In this sense, lower limb venipuncture may be useful if the suspicion of PFO is high and the passage of macrobubbles does not occur

with conventional puncture in the arm. The preparation of macrobubbles must be adequate; the Valsalva maneuver must be effective, and multiple infusions of agitated saline solution are recommended to make the diagnosis more sensitive.¹⁵ Nonetheless, transthoracic echocardiography with agitated saline infusion is an indirect diagnostic method that is not capable of describing the anatomy of the septum and the PFO.

Table 2 – RoPE score

Characteristic	Points
No history of	
Hypertension	1
DM	1
Stroke or TIA	1
Non-smoker	1
Proven cortical infarct	1
Age (years)	
18-29	5
30-39	4
40-49	3
50-59	2
60-69	1
>70	0

DM: diabetes mellitus; TIA: transient ischemic attack. A sum above 7 points indicates greater likelihood of cerebral ischemia due to PFO. Adapted from Thaler et al.⁹

Transesophageal echocardiogram

Transesophageal echocardiography offers excellent visualization of the interatrial septum, identifying the separation of the laminae of the septum primum and secundum and septal thickness. Using color Doppler at low speeds in the region of the foramen ovale, it is possible, in some cases, to identify the right-to-left flow. Even so, it is necessary to infuse agitated saline as in the transthoracic echocardiogram and to perform the Valsalva maneuver to separate the laminae of the interatrial septum, thus identifying the shunt. Adequate filling of the right atrium with macrobubbles and identification of movement of the septum towards the left atrium, with increased intra-abdominal pressure, determine the appropriate technique. The flow of macrobubbles must be monitored in the pulmonary veins to rule out extracardiac shunts (in which case the macrobubbles take more than 5 beats to opacify the left atrium and are visualized in the pulmonary veins).¹⁵

PFO risk stratification: essential measures and findings for defining high risk

- PFO height^{10,11} (Figure 1A): greater separation of the laminae of the septum primum and secundum > 2 mm.
- Tunnel length^{10,11} (Figure 1A): tunnel extension ≥ 10 mm.
- Angle between the inferior vena cava and the PFO¹⁰ (Figure 1B): angle ≤ 10°.
- Mobility of the interatrial septum:^{10,11} definition of an aneurysm, when the septal excursion is ≥ 10 mm from the septal plane or ≥ 15 mm in both directions (Video 1A).
- Prominent Chiari network and redundant Eustachian valve measuring ≥ 10 mm.
- Number of macrobubbles that pass into the left atrium (Video 1B): ≥ 20 macrobubbles.¹²

Nakayama et al.¹⁰ described a risk score based on the parameters described above and displayed in Table 4, where a score greater than or equal to 2 points is associated with a significant risk of ischemic stroke. This assists in therapeutic decision-making, in addition to alerting to possible complications during the procedure.

Monitoring the procedure: planning and choice of prosthesis

Percutaneous PFO closure is performed with the implantation of a double-disc device in the interatrial septum. Two versions of specific prostheses exist: one with discs with different diameters, where the right disc has a larger diameter (Figure 2D), and another version with discs of equal diameters, similar to cribriform prostheses for multi-fenestrated atrial septal defect. In both versions, the waist is extremely thin, in order to avoid deformation of the PFO tunnel.

Transesophageal echocardiographic monitoring is recommended for safety, efficacy, and evaluation of the final result of the procedure.¹⁶ In conjunction with fluoroscopy,

Table 3 – PASCAL score (the extended PFO-Associated Casual Likelihood Classification System)

Risk	Characteristics	Casual likelihood	
		Low RoPE score (<7)	High RoPE score (≥7)
Very high	Thrombus extending through the PFO	Definitive	Definitive
High	– PFO with aneurysm or large shunt – Pulmonary embolism or DVT before ischemia	Likely	Highly likely
Medium	– PFO + aneurysm – Large shunt through the PFO	Possible	Likely
Low	– Small shunt – Absence of aneurysm	Unlikely	Possible

DVT: deep vein thrombosis; PFO: patent foramen ovale; RoPE: risk of paradoxical embolism. Adapted from Thaler et al.⁹

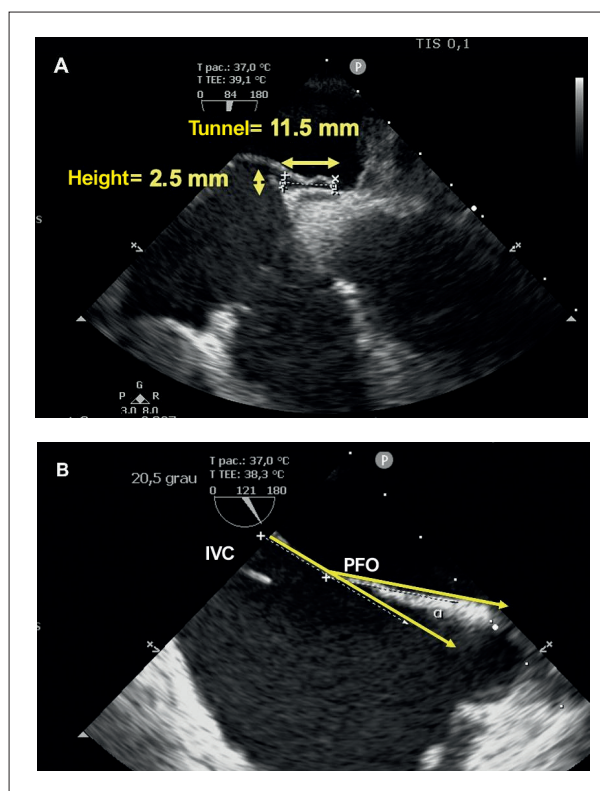
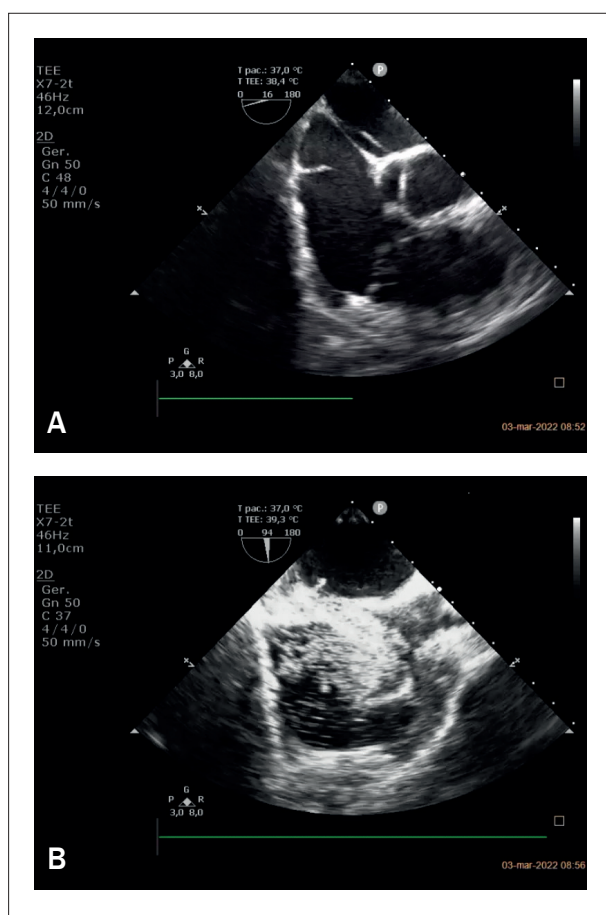


Figure 1 – Main measurements for risk assessment of PFO: A) PFO height and tunnel length. B) Angle between the inferior vena cava (IVC) and the PFO. Figures produced by Maria Estefânia Bosco Otto using Echonova's company image bank. IVC: inferior vena cava; PFO: patent foramen ovale.

transesophageal echocardiography allows visualization of catheters, guidewires, and the prosthesis. The use of the 3-dimensional modality better details the position of the device and its spatial relationship with adjacent cardiac structures. The guidance and information provided by



Video 1 – Septal mobility and passage of macrobubbles. A) Septal mobility before macrobubble infusion. B) Passage of more than 20 bubbles from the right atrium to the left atrium. Video edited by Maria Estefânia Bosco Otto using Echonova's company image bank. Links: http://abcimaging.org/supplementary-material/2024/3701/2023-0103_AR_video1A.mp4 and http://abcimaging.org/supplementary-material/2024/3701/2023-0103_AR_video1B.mp4.

Table 4 – PFO risk score

Variable	Points
Long tunnel ≥ 10 mm	1
Hypermobility of the interatrial septum	1
Prominent Chiari network or Eustachian valve	1
Large shunt with Valsalva maneuver (≥ 20 bubbles)	1
Angle between the IVC and PFO $\leq 10^\circ$	1

Score ≥ 2 considered high risk. IVC: inferior vena cava; PFO: patent foramen ovale. Adapted from Nakayama, 2019.¹⁰

transesophageal echocardiography are crucial for the various steps of the procedure (Figure 2; Video 2), which include the following:^{17,18}

- I. Crossing the PFO with a multipurpose catheter (Figure 2A).
- II. Introduction of the sheath into the left atrium through the PFO, using a rigid guidewire positioned in the left superior pulmonary vein.
- III. Loading and advancing the occluder prosthesis. Exposure and opening of the left disc (Figure 2B), which is retracted until it is seated on the left side of the interatrial septum. This is followed by the opening of the right disc in the right atrium (Figure 2C). The correct positioning of the device is checked, ensuring parallelism between the two discs, which must be visualized surrounding the septum. Systematic assessment of the device edges rules out interference with adjacent structures, such as the mitral valve, coronary sinus, aorta, and posterior wall of the atria. Color Doppler allows verification of possible persistence of a residual shunt on the edges of the device or inside it.
- IV. The “wiggle maneuver,” carried out by a careful movement, pushing and pulling the device, which is still connected to the delivery cable, to guarantee that the right disc and left disc do not shift into the contralateral chamber.¹⁹
- V. Prosthesis release (Figure 2D).

For the treatment to be successful, in the hemodynamics laboratory, adequate interaction and communication are indispensable between the interventionist and the echocardiographer, who must provide accurate information on the anatomy of the interatrial septum and the dimensions of the PFO. Nonetheless, standardization is still lacking to determine the appropriate size of the occluder device.²⁰ Furthermore, the nomenclature to describe the size of the PFO is still not uniform, and it is often based solely on 2-dimensional images.^{21,22} Recently, Datta and et al.²³ proposed a standardization of terminologies for PFO dimensions, as follows:

- **Tunnel length** (Figure 1A): distance between the opening of the foramen ovale in the right atrium and the left atrium.
- **Tunnel height** (Figure 1A): separation between the septum primum and septum secundum (minor axis of the oval opening).
- **Tunnel width** (Figure 3): size of the openings in the right atrium and left atrium, seen when viewing the PFO *en face* (major axis of the oval opening).

The width of the PFO tunnel is a crucial indicator, most appropriately assessed with 3-dimensional images. *En face* visualization of the PFO by 3-dimensional transesophageal echocardiography makes accurate assessment of the dimensions possible, and it may be particularly useful in cases of variant anatomy, such as double-orifice tunnels.

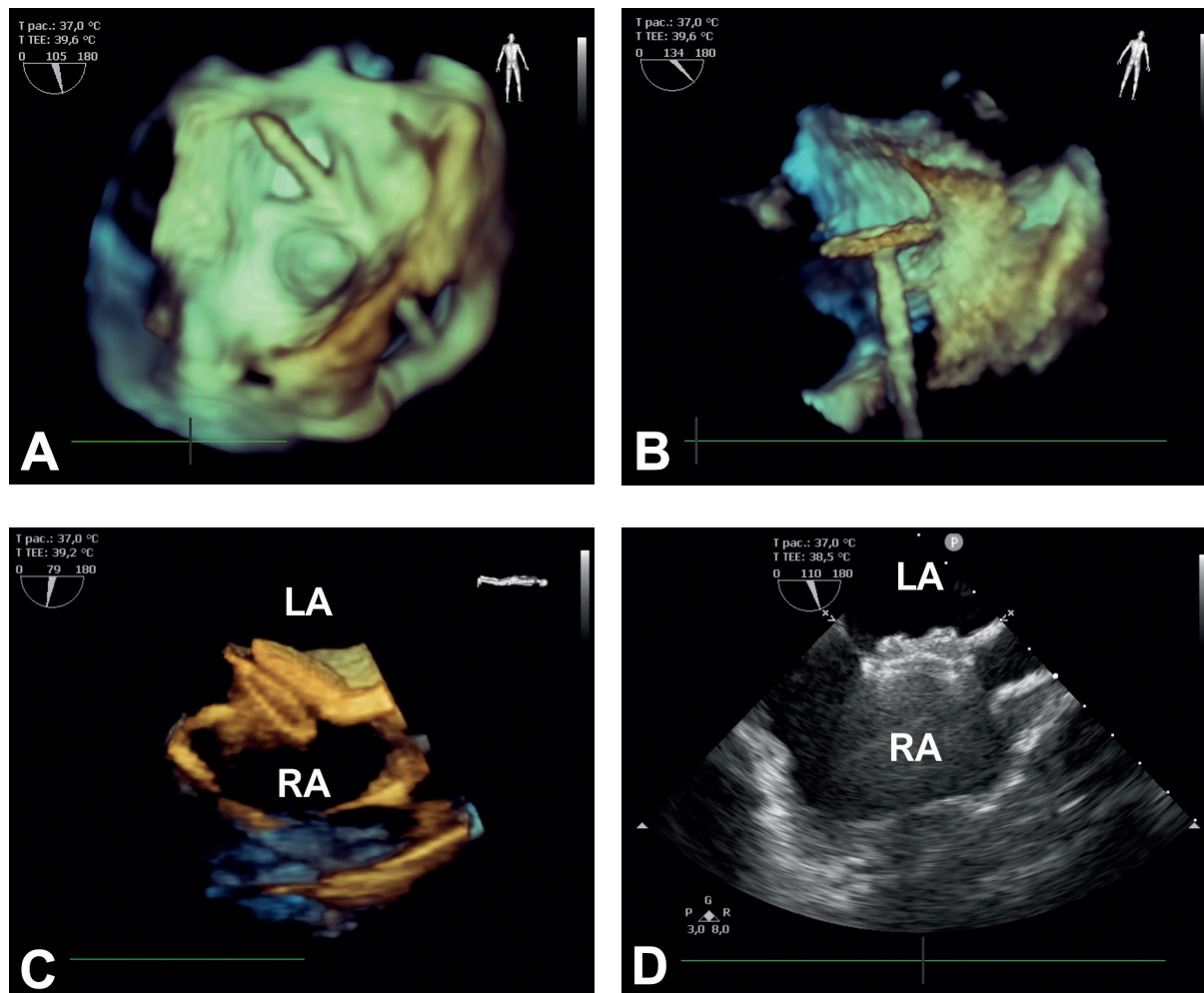
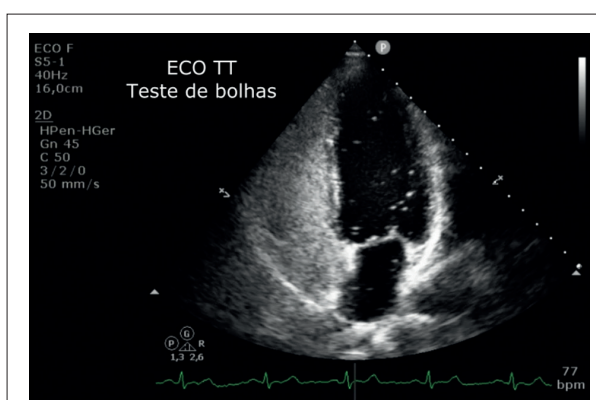


Figure 2 – Monitoring of percutaneous closure (Video 2): A) Introduction of a catheter into the left atrium (LA) through the PFO. B) Opening of the left disc of the prosthesis in the LA. C) Opening of the right disc in the right atrium (RA), with delivery cable connected to the prosthesis. D) Final appearance after releasing the double-disc prosthesis appropriate for PFO closure (right disc larger than the left disc). Figures produced by Fernando Melo Netto using Echonova's company image bank. LA: left atrium; RA: right atrium.

For device selection, some operators and manufacturers recommend balloon sizing, which aims to transform the elliptical shape of the PFO into a circular defect, where the diameter of the balloon waist approximates the width of the tunnel as assessed by 3-dimensional transesophageal echocardiography;²⁰ however, it is essential to avoid excessively stretching the PFO or damaging the interatrial septum with balloon inflation.²⁴ Recent instructions for the most widely used occluder (Amplatzer-PFO)²⁵ recommend the choice of larger prostheses according to the length of the tunnel, the presence of aneurysm, and thickness of the septum secundum (Table 5). Nonetheless, in the experience of several authors,^{22,23,26} the width of the PFO tunnel is the best parameter to guide selection of device size. In this approach, it is important for the diameter of the right disc of the prosthesis to exceed the width of the tunnel in the right atrium. If the diameter of the disc is



Video 2 – PFO, from diagnosis to closure. Case of a young patient with cerebral ischemia. Video edited by Fernando Melo Netto using Echonova's company image bank. L. O. C., female 38 years old 2 episodes of stroke Link: http://abcimaging.org/supplementary-material/2024/3701/2023-0103_AR_video2.mp4

smaller, there is a risk of thrombi penetrating through the margins of the device.

In addition to the PFO dimensions, it is essential to measure the anteroposterior diameter of the interatrial septum (midesophageal view of approximately 45°), in order to ensure that the disk can be adequately accommodated without impinging on surrounding cardiac structures, especially the posterior atrial wall or the aortic sinuses.²³

In situations where visualization of the tunnel is difficult due to the absence of separation between the septum primum and secundum, measurements must be performed during

the percutaneous procedure, after the introduction of a guidewire or catheter through the tunnel, inducing mechanical separation of the septa and allowing a more precise assessment of PFO dimensions²⁶ (Figure 3).

Intracardiac echocardiography is an alternative to transesophageal echocardiography during the procedure. Nonetheless, it has limitations, such as the cost of disposable probes, the need for specific training, potential risks related to femoral puncture, and the impossibility of multiplanar or 3-dimensional assessments, which impairs the measurement of the width of the PFO tunnel.

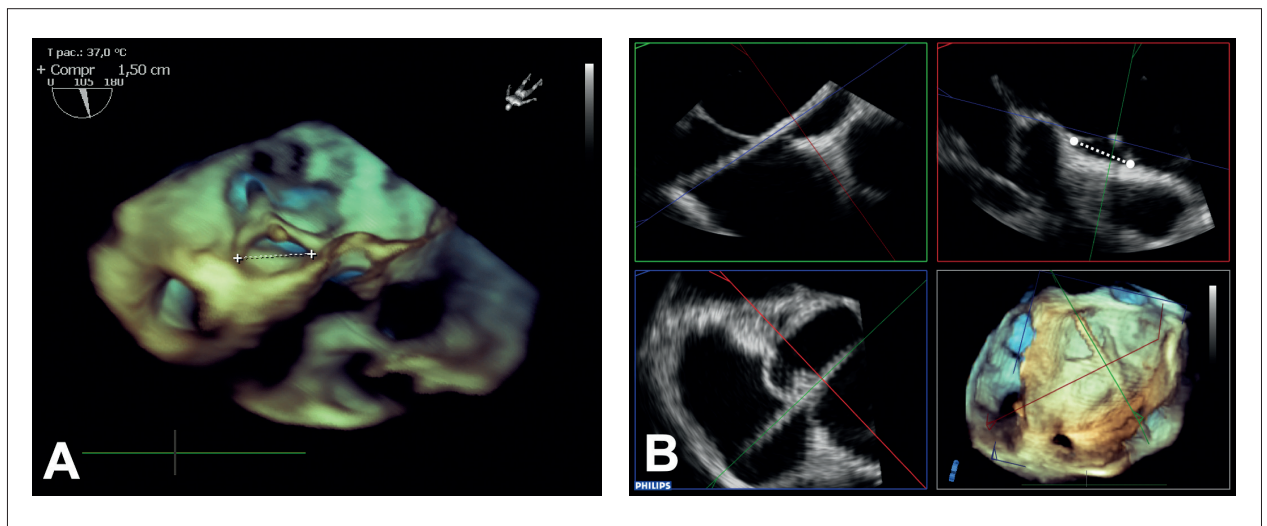


Figure 3 – Measurement of the width of the PFO tunnel using 3-dimensional transesophageal echocardiography: A) En face view of the PFO tunnel from the left atrium, after introduction of the catheter. The width of the tunnel corresponds to the dotted white line. B) Multiplanar reconstruction of the same image block to obtain PFO width. Figures produced by Fernando Melo Netto using Echonova's company image bank.

Table 5 – Recommendations for device dimensions

PFO morphology	Anatomical characteristics	Suggested Amplatzer™ Talisman™ occluder size
Simple PFO or PFO without prominent ASA PFO in which a secure device position and effective closure can be achieved when using the 25-mm device	1. Absence of ASA, long tunnel, and thickening of the septum secundum 2. Non-prominent ASA (total excursion < 20 mm) without long tunnel (≥ 10 mm in length), and without thickening of the septum secundum (≥ 10 mm in thickness)	25
Complex PFO PFO with one or more anatomical features that may complicate the ability to achieve safe device position and effective PFO closure when using the 25-mm device	1. ASA (excursion ≥ 10 mm) with a long tunnel (≥ 10 mm long) 2. ASA (excursion ≥ 10 mm) with thickening of the septum secundum (thickness ≥ 10 mm) 3. Prominent ASA with excessive mobility (total excursion ≥ 20 mm) 4. Lipomatous hypertrophy of the septum secundum (≥ 15 mm thick)	30 or 35
PFO with small anatomy Anatomy that is not appropriate for 25-mm device due to interference with adjacent cardiac structures	Septum primum length < 20 mm	18

ASA: atrial septal aneurysm; PFO: patent foramen ovale. Adapted from Abbott Laboratories. Amplatzer Talisman PFO Occluder Instructions for Use.²⁵

In most cases, the PFO has a typical anatomy that allows for effective and uncomplicated closure. Occasionally, specific characteristics of the septum make the procedure more complex and may increase the failure rate, for example: interatrial septal aneurysm; presence of multiple accessory fenestrations; long, rigid tunnel; lipomatous and hypertrophic septum secundum; prominent Eustachian valve and/or Chiari network; or misalignment of the interatrial septum ("spiral septum" or "double septum").¹⁷

In cases of aneurysm and/or hypermobility where there is significant separation (above 8 mm) between the septum primum and secundum, it is necessary to use a balloon to measure the stretched diameter of the tunnel. If it is equal to or greater than 13 mm, self-centering devices (with wide waists, for occlusion of interatrial communication) are preferable to non-self-centering devices (with a thin waist), due to the lower risk of residual shunt.^{27,28}

The presence of multiple fenestrations may require the implantation of several devices.²⁹ When there is no predominant defect, the preferred approach aims to cross the central defect and implant a thin-waisted device (cribriform prosthesis) to cover the peripheral fenestrations, depending on the distance between them and adjacent cardiac structures.

Suspicion of an excessively rigid and long septum primum (over 8 mm) arises when the tunnel opens less than 4 mm after the introduction of a guidewire or catheter, in which case the device may not seat properly. The frequently used technique is the implantation of the prosthesis through a transseptal puncture close to the tunnel opening, allowing adequate compression and positioning of the discs.³⁰

A septum secundum thicker than 7 mm is classified as hypertrophic. Mild hypertrophies do not usually complicate the procedure. However, if the thickness is greater than 15 mm, the risk of failure increases significantly. The use of a ventricular septal defect occluder prosthesis can obtain success.³¹

A prominent Eustachian valve, which interferes with the compression of the right disc against the interatrial septum, can be displaced with a pigtail catheter to help accommodate the device.³²

Complications

The use of transesophageal echocardiography is fundamental in assisting diagnosis, in therapeutic monitoring, and also in preventing and detecting immediate complications, including the following: assessment of mitral valve competence and patency of the coronary sinus, formation of intracardiac thrombi, early device embolization, and positioning of wires and catheters, thus avoiding perforation of the left atrial appendage, pericardial effusion, and cardiac tamponade.^{17,33-35}

The frequency and appropriate timing for echocardiographic monitoring still generate uncertainty. As

most devices are endothelialized in approximately 6 months, a bubble study may be considered at the end of this period, when the success rate is approximately 95%.³⁵ The results support the feasibility and safety of percutaneous closure, with no evidence of an increase in serious adverse events. Late complications, although rare, include device thrombosis, erosion of adjacent structures, prosthesis embolization, and endocarditis.^{36,37}

Arrhythmic complications, such as atrial fibrillation and flutter, have an incidence of approximately 3%. This can be attributed, in part, to manipulation of the catheter, passage of wires into the left atrium, and stretching of the atrial wall with the device. Atrial fibrillation generally manifests within the first 45 days after implantation, and it is a transient phenomenon in 76% of cases.³⁸

Conclusions

Percutaneous PFO closure has evolved with remarkable advances, driven by recent studies that support its benefits in preventing cryptogenic ischemic stroke. Risk stratification, considering clinical and anatomical aspects, together with the evolution of echocardiography, plays a crucial role in adequate patient selection and device choice. The need for strict monitoring, comprehension of potential complications, and careful assessment of individual characteristics are essential to optimize long-term outcomes. Ultimately, close collaboration between neurologists and cardiologists (clinicians, echocardiographers, and interventionalists) is fundamental to the success of the procedure and patient safety.

Author Contribution

Writing of the manuscript; critical revision of the manuscript for intellectual content; acquisition of images and video: Netto FM; Otto MEB.

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

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Study Association

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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