

# Echocardiographic Evaluation of Patients with Patent Foramen Ovale and Cryptogenic Stroke

*Avaliação Ecocardiográfica de Pacientes com Forame Oval Patente e Acidente Vascular Cerebral Criptogênico*

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## Abstract

Recent studies have indicated that patent foramen ovale (PFO) may cause cryptogenic stroke in young patients presenting anatomical conditions that can favor it and that transcatheter occlusion reduces the incidence of stroke versus clinical treatment. A transesophageal echocardiographic study with agitated saline injection associated with the Valsalva maneuver can evidence right-to-left shunt with high sensitivity (89%) and specificity (92%). The Risk of Paradoxical Embolism trial evaluated the clinical characteristics of stroke patients with PFO; established a risk score for cryptogenic stroke; and used a multivariate regression model to identify six variables including age, presence of cortical ischemia, diabetes, hypertension, stroke, and previous transient ischemic attack. The highest scores were observed in young stroke patients without vascular risk factors, and the lowest scores were identified in older patients with vascular risk factors in which the PFO appeared to be incidental. Anatomical PFO conditions predispose patients to systemic embolism (PFO separation > 2 mm, PFO tunnel > 10 mm, angle between the inferior vena cava and the PFO flap < 10°, shunt intensity with Valsalva maneuver, and presence of interatrial septal aneurysm and Chiari network or prominent Eustachian valve). PFO closure can prevent paradoxical embolism by decreasing the incidence of stroke in high-risk patients.

Recent studies demonstrating that transcatheter occlusion of the patent foramen ovale (PFO) reduces the incidence of cryptogenic stroke versus drug treatment<sup>1</sup> have increased interest in the relationship between cryptogenic stroke and the presence of PFO.

Echocardiographic examinations and autopsies identified thrombi crossing the foramen ovale, confirming this mechanism as a cause of paradoxical embolism, i.e., a venous thrombus passing into the arterial circulation through a right-left shunt. However, this echocardiographic visualization is rare, with few studies published<sup>2,3</sup> (Figure 1).

Some clinical studies demonstrated a PFO predisposition to cause paradoxical embolism. Patients with diabetes, systemic

arterial hypertension, and coronary artery disease present a low PFO predisposition to cause paradoxical embolism. On the other hand, a history of deep venous thrombosis, pulmonary embolism, pulmonary hypertension, prolonged travels, the Valsalva maneuver preceding the onset of stroke symptoms, migraine, and sleep apnea has been described as an independent risk factor for the association between PFO and cerebrovascular events.<sup>4</sup>

Although visualization of thrombi in the foramen ovale is uncommon, epidemiological observation leads to the belief that PFO is responsible for a considerable number of strokes.<sup>5</sup>

An autopsy study of 965 normal hearts showed a PFO prevalence of 27%, with similar distributions in men and women. This prevalence decreases with age, being 34% in people aged under 30 years, 25% between 30 and 80 years, and 20% over 80 years.<sup>6</sup> However, cryptogenic stroke patients show a particularly high prevalence of up to 40% in patients aged under 55 years.<sup>7</sup>

It is important to note that the presence of PFO in cryptogenic stroke patients is not the only etiology for paradoxical embolism. Other mechanisms can cause it, such as undetected atrial fibrillation, cardiac tumors (myxoma and fibroelastoma), presence of spontaneous echocardiographic contrast in the left atrium, rheumatic mitral valve disease, mitral valve ring calcification, biological and mechanical heart prostheses, hypercoagulability states, and ascending aorta atheroma.<sup>8</sup>

An echocardiographic study is part of the routine PFO evaluation, mainly transesophageal echocardiography (TEE) with agitated saline solution (bubble). A small shunt is considered when three to 10 bubbles pass, a medium shunt when 10–30 bubbles pass, and a large shunt if more than 30 bubbles are counted in the first beats after the injection.<sup>9</sup>

In addition to shunt detection, TEE evaluates the anatomical characteristics of PFO and the differential diagnosis with atrial septal defect and pulmonary shunt.<sup>10,11</sup>

Studies comparing TEE with bubbles and autopsy findings reported a sensitivity of 89% and a specificity of 92%, with autopsy being considered the gold standard.<sup>12</sup>

The performance of an efficient Valsalva maneuver associated with the use of bubble solution is extremely important. This aspect is often overlooked, especially when the test is performed under deep sedation, which can result in a false-negative result. The use of superficial sedation or local oropharyngeal anesthesia is recommended with bubble solution injection to diagnose PFO.<sup>13</sup>

Transcranial Doppler showed more sensitivity but less specificity than TEE in PFO diagnosis. This lower specificity

## Keywords

Echocardiography; Foramen Ovale, Patent; Stroke.

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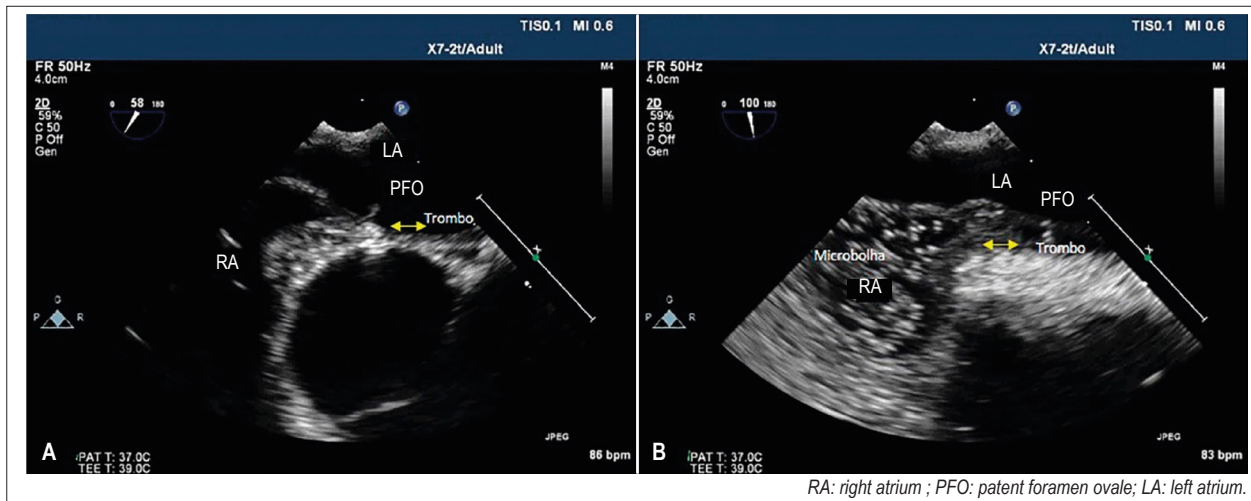
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## Point of View



**Figure 1** – Transesophageal echocardiogram showing the presence of a thrombus in the patent foramen ovale (PFO) without evidence of macrobubble passage. AD: right atrium; AE: left atrium.

is justified by insensitivity to a differential diagnosis between cardiac and pulmonary shunt in addition to the limited diagnosis of anatomical changes that favor the presence of PFO, such as the presence of an interatrial septum aneurysm and septal mobility.<sup>14</sup>

As for the best therapeutic option for cryptogenic stroke patients (drug therapy or percutaneous closure), the CLOSURE trial in 2012<sup>15</sup> and the RESPECT<sup>16</sup> and PC trials<sup>17</sup> in 2013 showed no benefits of percutaneous therapy for PFO closure compared to drug therapy. However, the randomized CLOSE,<sup>18</sup> REDUCE,<sup>19</sup> and RESPECT<sup>20</sup> trials determined a therapeutic conduct change in 2017, as they demonstrated that percutaneous PFO closure is superior to drug treatment in preventing cryptogenic stroke in a specific population. After this conduct change, several studies have aimed to improve and more precisely determine which patients are most likely to benefit from interventional treatment.

The Risk of Paradoxical Embolism<sup>21</sup> study evaluated the clinical characteristics of cryptogenic stroke patients with PFO and proposed a risk score to stratify patients by age and the presence or absence of vascular risk factors. Using clinical and radiological data from 3,000 patients, a multivariate regression model identified six variables associated with cryptogenic stroke, establishing a score with 10 points to stratify the probability of PFO being associated with stroke or being an incidental event. The variables analyzed included age, presence of cortical stroke on an imaging study, and presence or absence of diabetes, systemic arterial hypertension, stroke, or previous transient ischemic attack. The risk score was calculated using these 10 variables for a period of 2 years in each group (Table 1).

Young patients with superficial stroke and no vascular risk factors have a high score. The prevalence of PFO increases from 23% in patients with 0–3 points to 73% in patients with 9–10 points. High scores are seen in young patients with few or no traditional risk factors experiencing superficial cerebral infarctions. The presence of PFO in patients with low scores, who are older, and who have vascular risk factors suggests an

incidental onset. The risk of stroke or transient ischemic attack is estimated for a period of 2 years in each group<sup>22</sup> (Table 2).

A recent study showed that some anatomical characteristics of PFO predispose patients to the formation and passage of

**Table 1** – Risk of Paradoxical Embolism (RoPE) score.

Characteristics	Points
No history of hypertension	1
No history of diabetes	1
No history of stroke or TIA	1
Non-smoker	1
Cortical ischemic stroke on imaging test (CT or MRI)	1
Age in years	
18-29	5
30-39	4
40-49	3
50-59	2
60-69	1
≥70	0

Source: Thaler et al.<sup>21</sup> CT, computed tomography; MRI, magnetic resonance imaging; TIA, transient ischemic attack.

**Table 2** – Risk of stroke.

Total points	Risk of stroke being related to PFO (%)
0-3	0
4	38
5	34
6	62
7	62
8	84
9-10	88

Source: Kent et al.<sup>22</sup> PFO, patent foramen ovale.

thrombi from the right to the left atrium, causing systemic embolisms.<sup>23</sup> These characteristics are:

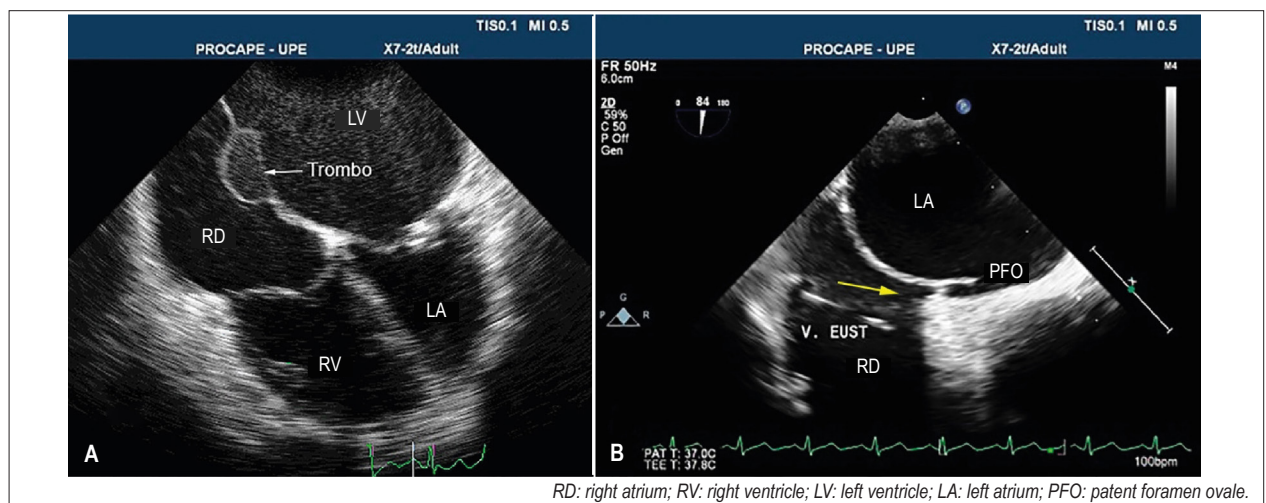
- PFO width: a maximum separation between the septum primum and the septum secundum > 2 mm is considered large. A study comparing 58 patients undergoing PFO occlusion after cryptogenic stroke with 58 patients with asymptomatic PFO evaluated by TEE reported a wider PFO in the stroke group ( $p < 0.001$ ).<sup>24</sup>
- Long tunnels > 10 mm occur more frequently in cryptogenic stroke patients (46% versus 17%,  $p < 0.01$ ).
- The degree of right-left shunt is evaluated at rest and after the Valsalva maneuver using agitated saline contrast. The number of bubbles is counted in a single frame, indicating an important shunt with greater risk of stroke when greater than 20 (16% versus 5%,  $p < 0.06$ ).
- The angle between the inferior vena cava (IVC) and the oval foramen flap must also be measured. An angle < 10° indicates a greater risk for stroke.
- Interatrial septal aneurysm is defined by the presence of redundant mobile tissue in the oval fossa region with a 10–15 mm phasic excursion during breathing.<sup>25</sup> Its prevalence on TEE is 2.2% in the general population.<sup>26</sup> Stroke patients present a high prevalence of septal aneurysm, 7.9–15% in patients with possible embolic stroke and 28% in patients with ischemic brain events and normal carotid arteries.<sup>27</sup> Two mechanisms have been proposed as responsible for paradoxical embolism caused by aneurysm or hypermobility of the interatrial septum:
  - As this aneurysm is frequently associated with PFO, paradoxical embolism would occur through the passage of the thrombus from the right to the left atrium, through the PFO (Figure 1). Intracardiac shunt has been identified in 78% of patients with aneurysms. There is also an interatrial shunt due to PFO in 54–84% of stroke patients with a septal aneurysm.
  - Patients with atrial septal aneurysm without an intracardiac shunt can present small fibrin and platelet thrombi formed on

the left side of the septum that break loose with aneurysm oscillation and cause a systemic embolism (Figure 2A).

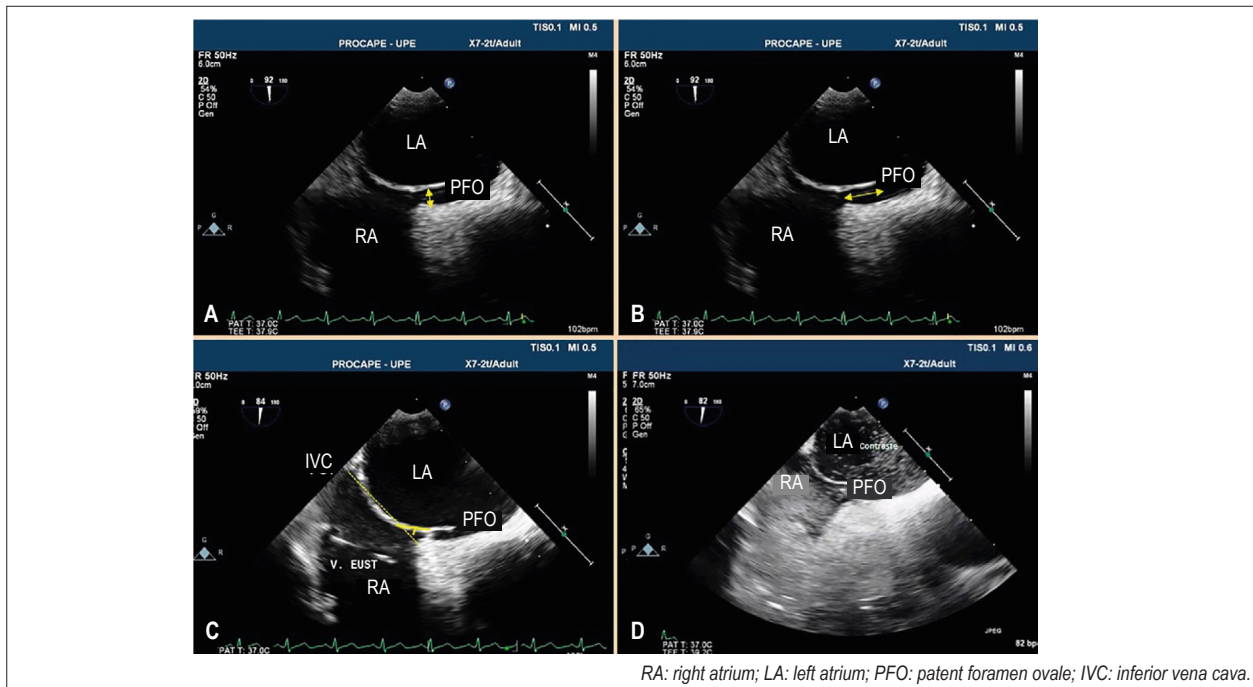
- Eustachian valve and Chiari network: The Eustachian valve is located at the junction between the IVC and the right atrium, being redundant in some people (Figure 2B). The Chiari network consists of a mesh of filamentous and fibrous structures in the right atrium that originates in the region of the Eustachian and Thebes valves, is close to the IVC opening and inserted in the right atrium wall or in the interatrial septum. A review study of 1,436 TEEs detected the presence of the Chiari network in 2% of the tests, of which 83% had PFO and 27% had interatrial septal aneurysm. The Chiari network occurs more frequently in patients undergoing TEE due to cryptogenic stroke than in studies conducted for other indications (4.6% versus 0.5%).<sup>28</sup> These structures can direct the flow, which arrives through the IVC directly to the interatrial septum, favoring foramen ovale persistence, interatrial septum aneurysm, and, indirectly, facilitating a paradoxical embolism. PFO with a large right-to-left shunt was more frequently identified in patients with a Chiari network (55% versus 12%).<sup>29</sup>

The multivariate analysis of these observations showed that cryptogenic stroke patients with PFO had wider (>2 mm) and more extensive (>10 mm) PFO (Figures 3A and 3B), more mobile interatrial septa, prominent Eustachian valves and Chiari network, and a PFO-IVC angle < 10° (Figure 3C). These factors are independent predictors of ischemic brain events<sup>23</sup> (Table 3). A risk score for PFO being responsible for paradoxical embolism in patients with stroke was developed based on the echocardiographic analysis of these anatomical data (Table 4).

High scores are seen in young patients undergoing superficial cerebral infarctions with few or no traditional risk factors. Since affected patients are more likely to have low scores, be older, and have vascular risk factors, PFO may have an incidental PFO onset not causally related to an ischemic event. The risk of stroke or transient ischemic attack is calculated for a period of 2 years.



**Figure 2** – A: Transesophageal echocardiogram showing an interatrial septal aneurysm without evidence of PFO with the presence of a thrombus on the left side. B: Transesophageal echocardiogram showing the position of the Eustachian valve directing the flow towards the PFO (arrow). LA: left atrium; AD: right atrium; LV: left ventricle; RV: right ventricle; FOP: patent foramen ovale; V. Eust: Eustachian valve.



**Figure 3** – Characteristics of the patent foramen ovale (PFO). (A) PFO width, (B) PFO extension, (C) Angle between PFO and the inferior vena cava (IVC), (D) PFO with macrobubble injection showing shunt between the right atrium (AD) and the left atrium (AE). FOP: patent foramen ovale.

**Table 3** – Risk of stroke caused by patent foramen ovale.

Variable	Points
Long PFO tunnels (>10 mm)	1
Interatrial septum hypermobility	1
Extensive Eustachian valve or Chiari network	1
Large shunt during the Valsalva maneuver	1
PFO-IVC angle < 10°	1

Source: Nakayama et al.<sup>23</sup> IVC, inferior vena cava; PFO, patent foramen ovale.

**Table 4** – Risk of stroke.

Score	Risk of stroke (%)
0	5
1	17
2	80
3	87
4	89

AVC: acidente vascular cerebral.

## Conclusion

Percutaneous PFO closure can prevent paradoxical embolism and reduce the risk of recurrent cryptogenic stroke in high-risk patient groups. As a result, risk scores were developed to determine which patients will benefit from interventional therapy. The first observational study evaluating anatomical data by TEE allowed the development of a risk score that defines which patients with PFO may have cryptogenic stroke, for whom percutaneous closure would be indicated.<sup>23</sup>

New echocardiographic parameters for the evaluation of PFO open new diagnostic, prognostic, and therapeutic perspectives for young patients at risk of cryptogenic stroke as well as for patients aged over 60 years.

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## Authors' contributions

Research concept and design, data collection, analysis and interpretation, manuscript writing, critical review of the manuscript for important intellectual content: CAM Silveira; data analysis and interpretation, manuscript writing, critical review of the manuscript for important intellectual content: JM Del Castillo.

## Conflict of interest

The authors have declared that they have no conflict of interest.

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