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Patent foramen ovale and cryptogenic stroke: from studies to clinical practice

Position paper of the Italian Chapter, International Society Cardiovascular Ultrasound

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SUMMARY

Background: Over the last two decades the interest on patent foramen ovale (PFO) as a cause of cardioembolism in cryptogenic stroke has tremendously increased, thanks to the availability of better techniques to diagnose cardiac right-to-left shunt by ultrasounds and of percutaneous means of PFO treatment with interventional techniques. Many studies have been published that have attempted to define diagnostic methodology, prognosis, and optimal treatment (pharmacological or percutaneous closure) of PFO patients with cryptogenic stroke. Unfortunately, even today, definitive evidence is still lacking, and clinical management is not consistent among cardiologists. **Aims:** This review aims to evaluate the role of PFO in cryptogenic stroke, the diagnostic accuracy of transcranial Doppler, contrast transthoracic and transesophageal echocardiography in the diagnosis of left–fright shunt and PFO; and discuss the indications to medical treatment and percutaneous closure of PFO. **Methods:** All studies published in the literature on PFO and cryptogenic stroke are considered and discussed. **Results:** We define an appropriate diagnostic and clinical management of PFO patients with cryptogenic stroke. **Conclusion:** After many years of interest on PFO and many concluded studies, there are still no definitive data. However, we are on good track for an appropriate management of PFO patients and cryptogenic stroke.

Review criteria

PUBMED cited articles on patent foramen ovale and cryptogenic stroke.

Message for the clinic

Purpose of this article was to discuss current knowledge derived from clinical studies and provide practical clinical guidelines for the daily management of patients with PFO. Finally, some practical key points that can be useful for different specialists for the clinical management of PFO patients were discussed and listed.

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None.

Introduction

Patent foramen ovale (PFO) is a common interatrial septal anomaly; clinical studies report a prevalence of PFO in about 25% of the general population, which increases to over 50% in patients with cryptogenic stroke (1).

The relationship between PFO and stroke related to paradoxical embolism has been studied extensively in the last two decades. Several observational studies have appeared in the literature, so for a total of thousands patients being evaluated. These studies have described a clear relationship between PFO and stroke in younger patients (aged < 55 years) with no other identifiable causes. However, it remains largely undefined which subject with PFO will eventually have a first-ever stroke or recurrent event. Furthermore, there are no certainties about the optimal therapy to be used (medical or closure), and the proper diagnostic work up is not completely consistent.

In this respect, crucial information is still missing for several reasons:

- the high prevalence of PFO in the general population, and by contrast the relatively rare frequency of embolic stroke
- the possibility of a mere probabilistic, non-causal association between PFO and stroke
- the unclear knowledge of all factors that, alone or in combination, define a higher risk of embolisation among PFO subjects
- the publication of only three randomised clinical trials of percutaneous PFO closure, with a relatively small number of patients studied, short-term follow-up, and unclear results.

Natural history and pathophysiology of PFO

Patent foramen ovale is a flap-like opening between the atrial septum primum (on the left) and secundum (on the right) at the fossa ovalis. During fetal life, the foramen ovale plays a physiologic role, having the purpose of directing most oxygenated

Figure 1 Patent foramen ovale anatomy. The septum primum and secundum are separated by a one-way channel with right-to-left shunt

placental blood from right to left atrium, and hence into the systemic circulation, excluding the pulmonary bed. Blood shunting is favoured by the presence of other embryonic structures: the Eustachian and Thebesian valves and the Chiari network. After birth, distension of the alveolar parenchyma reduces right atrial pressure, while left atrial pressure increases, allowing functional closure of PFO. Eustachian and coronary sinus valves regress and blood flow from the inferior vena cava is directed into pulmonary circulation. Over the first year after birth, the tunnel is 'welded' by a fibrous process, and the septum is anatomically closed.

In adults, persistence of PFO results from failure to close, with presence of right-to-left shunt (Figure 1); the mechanism of persistence is not clear, but pressure gradient between atria can play a fundamental role (2,3). Failure of Eustachian valve involvement and persistence of Chiari network (mobile, net-like structures occasionally seen in right atrium) increase the width of tunnel and shunt and identify an increasing risk of paradoxical embolism (4,5). Autoptic and cardiac imaging studies report a prevalence of PFO ranging from 14.9% to 27% in the general population (3,6).

Patent foramen ovale can also be associated with atrial septal aneurysm (ASA) (7–10). This is a mobile protrusion of the fossa ovalis into either or both atria, and it is defined by > 10 mm excursion in the septum (Figure 2) (11,12).

In the general population, ASA prevalence is about 1% at autopsy series and 2.2% in transesophageal echocardiography studies, while in stroke patients, ASA has been found in 50–85% of cases (7–9,13).

Many studies have demonstrated that ASA alone increases the risk of first-ever stroke and recurrence and the combination PFO and ASA constitutes a particularly high-risk condition, with a 16-fold increase in relative risk comparing ischaemic stroke with no-stroke control subject and of 17-fold increase in relative risk comparing cryptogenic stroke with stroke of known cause (aged < 55) (1).

The shunt through PFO is a valve mechanism with unidirectional flow; in case of PFO+ASA, the septum is stretched by blood flow and it can develop multiple little defects (fenestrated septum) with bidirectional shunt (5).

Several mechanisms have been invoked to explain how PFO can cause paradoxical embolism:

- The most common mechanism is the 'preferential route' for embolic transit from the systemic venous circulation to the cerebral circulation of platelets aggregates, thrombi, gas bubbles or other particulate matter. In this case, PFO does not have an active role, but it allows emboli to transit through the interatrial opening, thus inducing paradoxical embolism (1,14,15).
- In some cases, particularly in patients with ASA, the PFO could be a 'nidus' for potentially embolic thrombi that once formed are released into the systemic circulation during a temporary or permanent increase in right atrial pressure (16–20).
- Finally, the PFO could be a 'trigger' for potentially embolic supraventricular arrhythmias (21). Some studies demonstrated that in patients aged < 55 years with cryptogenic stroke atrial vulnerability is present in 61% of the ASA, in 57% of PFO and in 60% of PFO+ASA. The mechanism of atrial arrhythmias is thought to be stretching of atrial septum (22,23).

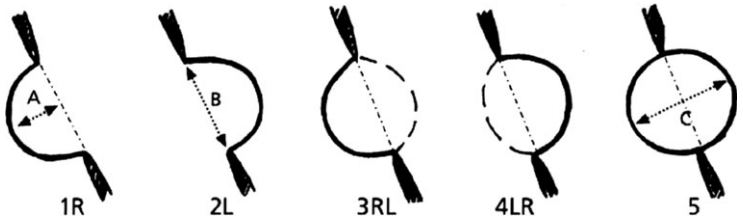

Figure 2 Classification of ASA: According to the fluctuation from the midline of the septum are displayed five types of aneurysms. 1R fluctuation only in the right atrium, 2L fluctuation exclusively in the left atrium, 3RL fluctuation prevailing in the right atrium, 4LR fluctuation prevailing in the left atrium, 5 fluctuation in both atria (11)

Finding a thrombus straddling on PFO (impending stroke) unequivocally demonstrates the causality with systemic ischaemic events; the relationship between atrial fibrillation and stroke is well known; in all other cases – which represent the vast majority – however, the relationship between PFO and systemic ischaemic events is not causal but only probabilistic.

Diagnosis

Transcranial Doppler (TCD), transthoracic (TTE) and transesophageal (TEE) echocardiography are the main techniques available for PFO diagnosis and risk stratification. For detection of right-to-left shunt, all these ultrasound techniques rely on the injection of microbubbles contrast (agitated blood–saline/air–saline mixture) into a peripheral vein under basal condition and upon release of Valsalva manoeuvre, or alternatively/additionally by coughing (24,25). These provocative manoeuvres are aimed at to increase the right atrial pressure and facilitate the PFO opening. TTE and TEE are specific investigations for PFO and can carefully assess the functional status of the shunt. TEE represents the gold standard because it directly shows the interatrial tunnel and accurately visualises the PFO anatomy.

Transcranial Doppler is a non-invasive technique with very high sensitivity (98%), specificity (80%) and diagnostic accuracy for shunts; its limitation is that it does not differentiate between intracardiac and pulmonary shunts, which can occur in many pulmonary diseases (26). This tool demonstrates right-to-left shunt by detecting the presence of contrast as 'hits'. Hits are hyperintense signals superimposed to the Doppler spectrum of middle cerebral artery flow velocity. The amount of detected signals, within 30 s after contrast injection, is proportional to the size of the shunt (27,28) (Table 1).

Table 1 Transcranial Doppler and right-to-left shunt quantification

Shunt size	Microbubbles	Signal description
No	≤ 1	
Small	< 10	
Moderate	10–25	
Large	> 25	Shower Curtain
		Signal so intense/ prolonged cannot count microbubbles

Transthoracic echocardiography detects with high accuracy all causes of cardioembolic heart diseases (valvular heart diseases, left ventricular dysfunction, left atrial dilatation, intracardiac thrombosis, endocarditis, etc.) and visualises the atrial septum, ASA, and other right atrial structures such as Eustachian valve (especially if prominent) and Chiari network. TTE does not show directly the PFO, but using contrast with second harmonic imaging, it has proved useful for diagnosis and evaluation of the extent of shunt, with a sensitivity equivalent to TEE in the detection of PFO (90% in all shunts, 94% in large shunts), while being more cost-effective (29,30).

Under normal conditions and in the absence of vascular dilatation, the contrast injection opacifies right atrium and bubbles are not observed in the left atrium because lung capillaries act as filters; when the PFO is present, bubbles cross through the atrial tunnel into the left atrium quickly. The intracardiac shunt is defined positive in the presence of bubbles visualised in left atrium within three cardiac cycles; conversely, intrapulmonary shunting can be demonstrated by contrast TTE when bubbles are visualised in the left atrium within 3–6 beats after being noted in the right side of the heart (31).

The intracardiac shunt is defined mild if < 10 bubbles are counted and large with ≥ 10 microbubbles (Figure 3). In some cases, persistence of Eustachian valve can create a false-negative result if contrast is injected through an upper extremity vein; in these cases, the injection via femoral vein can enhance PFO detection (32,33).

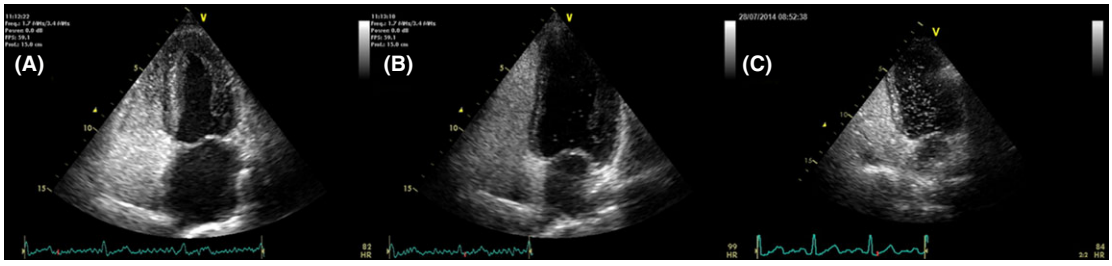

Figure 3 Transthoracic echocardiography with bubbles test: Right chambers are completely opacified by contrast medium. (A) No right-to-left shunt. (B) Positive bubbles test for mild shunt (< 10 bubbles count). (C) More than 10 bubbles are visualised in left chambers like as large shunt

Table 2 Morphological and functional information required for a complete PFO study

Gathered information	Information	Benefit
Size	Morphological (tunnel size)	Useful for closure
	Functional (shunt size)	Risk stratification
Wall features	Septal thickness	Useful for closure
	Overlap length (short, long)	
	Relation between two septa (simple, complex)	
Location	Anterior	Useful for closure
	Posterior	
	Superior	
PFO + ASA	Combination PFO + ASA	Risk stratification
PFO + other structures	Thrombi	Risk stratification
	Chiari network	
	Eustachian valve	

PFO, patent foramen ovale; ASA, atrial septal aneurysm.

Transesophageal echocardiography has high sensitivity and specificity in the diagnosis of PFO (15,16). This approach visualises closely the PFO anatomy, displaying PFO presence, location and size, wall features, presence of other septal defects, ASA, other atrial structures and thrombi (Table 2). The size of shunt can be visualised both with colour Doppler and contrast. The colour Doppler has the advantage of providing direct evidence of right-to-left shunt location and to verify the presence of a fenestrated septum. The 'bubble' test (i.e. contrast) is more accurate and represents the best diagnostic tool; however, sedation can compromise an effective Valsalva manoeuvre (17,21).

MRI and CT scans, which are considered in many cardiac diseases as the gold standard techniques, do not provide diagnostic information for PFO. Both can be useful to show the extent and kinesis of the ASA, but their use in clinical practice is not recommended (34).

Anatomical risk stratification

Careful instrumental assessment allows to stratify the risk of PFO and check the probability that is responsible of first-ever stroke and recurrence.

Currently, anatomical factors that increase the risk are considered: (i) a large PFO (> 4 mm); (ii) a long tunnel with length > 10 mm; (iii) a right-to-left shunt already visible under basal conditions, especially if associated with ASA; (iv) the persistence of atrial structures such as prominent Eustachian valve (size > 10 mm) and Chiari network (1,14).

Diagnostic flow chart

As already described, each diagnostic tool has its accuracy and features in the evaluation of shunt and/or PFO anatomy. Although TEE is regarded as the mainstay for PFO detection, current echo machines equipped with harmonic imaging allow the contrast TTE (cTTE) an equivalent sensitivity to visualise right-to-left shunt through a PFO. Thus, in our opinion, the good screening value of TCD (the most sensitive test for right-to-left shunt) and cTTE (accurate test for PFO) does not justify the extensive use of TEE. This tool is useful in cases in which TTE is negative or when it is necessary to obtain a better definition of PFO anatomy in preparation for percutaneous closure.

PFO and relationship with stroke

There are many evidences that PFO is the culprit of cryptogenic stroke/TIA.

First-event stroke

Although in most cases the role of PFO in stroke is only probabilistic, the relationship between PFO and cryptogenic embolism is supported by the significantly higher prevalence of PFO in stroke (40%) than in controls (25%) and is highest in cryptogenic stroke (56%) than in stroke with identifiable cause (21%) (35,36).

Stroke patients aged < 55 years had a PFO prevalence six times greater than that of patients with other forms of stroke (1,10,37,38). Despite this, prospective studies have not clearly demonstrated an association, and PFO has not been found an independent risk factor for future cerebrovascular events in the general population (39). This is not surprising, since, as already remarked, the prevalence of PFO is high in the general population and only a small number of people with PFO may have an additional factor that increases the risk of stroke. Therefore, primary prevention of paradoxical embolism in subjects with PFO is not recommended (40).

Recurrent stroke

There is no clear evidence about the role of PFO in recurrent stroke. On one hand, some studies reported that the presence of PFO increases the risk of recurrent stroke (1); on the other hand, pooled analysis of prospective studies did not find an increased risk of recurrence among cryptogenic stroke patients with PFO compared with those without PFO (10,26,41). However, although low, the risk of recurrent stroke after a first cryptogenic event justifies a search for an effective preventive therapy,

especially in patients considered to be at high risk. To stratify such patients, the RoPE (Risk of Paradoxical Embolism) risk score has recently been proposed (42). The RoPE investigators used clinical components of 12 large studies (3023 patients analysed overall) and constructed an intuitive index that in the absence of risk factors (arterial hypertension, diabetes, no previous stroke/TIA, non-smoker), with young age and cortical cerebral lesions, identifies the stroke related vs. incidental PFO in cryptogenic stroke (42).

Optimal therapy of PFO patients

Medical therapy

Optimal management of paradoxical embolism is still controversial. Numerous uncontrolled studies have shown a benefit of medical therapy. PICCS study and a meta-analysis of studies carried out around 2000s had already shown that warfarin is superior to antiplatelet therapy in preventing recurrent ischaemic events (26,43). However, after balancing effectiveness with the higher haemorrhagic risk and need for more complex monitoring and therapeutic adjustments of warfarin, the two therapeutic choices are considered largely equivalent (1,43–46).

Medical treatment is not free from adverse effects; the most notably is an increasing risk of bleeding with no significant differences between aspirin and warfarin (1.5–2.2 per 100 patients/year) (26,44); another is the rate of recurrent stroke (1.6 events per 100 patients/year) (43). Finally, the lack of patient's compliance represents, itself, a major limitation of medical therapy.

Percutaneous closure

Percutaneous closure of PFO has rapidly become quite popular. This is due to the attractiveness of the idea of effectively eliminating the mechanism for paradoxical embolism, its safety and feasibility (47,48). However, it must be considered that closure has significant costs, that complication rate is reported at approximately 10%, that complete closure does not always occur in 13% of cases, and that early recurrence rate of ischaemic strokes/TIAs varies between 0% and 3.4% (49–51). A definitive answer on the stringent indications for percutaneous closure can only come through solid evidence-based information that, at present, is still insufficient.

Over the years, a few randomised trials have been published comparing the effectiveness of percutaneous closure with medical therapy (51–53). Lack of properly performed randomised trials is mostly due to the difficulty of enrolment, as patients typically prefer to have a device implanted, avoiding the inconvenience of a long-term medical treatment (especially if on warfarin), to the obstacles at performing blinded trials, and with a personal belief on the part of physician and patients that closure could represent the 'cure of the problem' (54–57).

Currently, data from three randomised trials are available. The CLOSURE I enrolled 909 patients randomised to medical therapy or closure with STARflex; the primary end-point was recurrence of TIA/stroke (51). The RESPECT trial enrolled 980 patients randomised to medical therapy or closure with Amplatzer; primary end-point was fatal and non-fatal stroke (52). The PC trial enrolled 414 patients randomised to medical therapy or closure with Amplatzer; primary end-point was death, TIA, stroke and peripheral embolism (53). All three studies have not provided conclusive data and were subjected to broad discussion. In fact, while there was a favourable trend favouring closure which was statistically significant at 'per patient'/'as-treated' analysis, all studies have failed to demonstrate the superiority of percutaneous closure at 'intention-to-treat' analysis.

These findings are confirmed by more than 12 meta-analyses: only one on observational studies and the others on controlled randomised trials (58–61). These meta-analyses performed as both 'intention to treat' and 'per protocol basis' showed a possible benefit of the transcatheter closure that was borderline statistically significant compared with medical therapy. For this reason, PFO closure is not currently recommended as first-line management (62,63).

Management of patients with PFO and cryptogenic stroke: current guidelines and the Italian position paper

The 2011 American Heart Association/American Stroke Association guidelines stated that antiplatelet therapy is the treatment of choice for stroke or TIA in patients with PFO, whereas the use of vitamin K antagonists is reasonable only in high-risk patients having other indications for oral anticoagulation, such as hypercoagulable states (62). In 2012, the American College of Chest Physicians has similarly recommended the use of antiplatelet therapy for PFO patients with cryptogenic stroke (63); those guidelines suggested to use vitamin K antagonists or to consider percutaneous closure over aspirin only for those patients who have experienced recurrent events despite aspirin or have evidence of deep vein thrombosis.

A significant contribution to the controversial issue of the optimal management of patients with PFO and cryptogenic stroke has been recently given by nine Italian Cardiologic, Neurologic, and Hematologic

societies, which have jointly published a position paper in order to allocate treatments individually on the basis of the available evidence of both randomised and non-randomised studies, also taking into account the strengths and limitations of each conclusion (64). This strategy requires a multidisciplinary approach to estimate the probability of recurrence of stroke and the probability of any association between cerebrovascular accidents and PFO.

Italian chapter of international society cardiovascular ultrasound position:

Patent foramen ovale is a common abnormality of the atrial septum, and in itself, it is not yet considered a pathological finding but only a normal anatomical variant. In general population and in primary prevention, the PFO screening is not explainable.

The incidental (casual) discovery of ASA on TTE performed for other reasons does not justify the search for a PFO (65).

Patent foramen ovale is not the primary cause for stroke, and most individuals will remain asymptomatic throughout their life and only a small percentage of subjects with PFO will experience a cerebral ischaemic event. Hence, treatment in primary prevention is not recommended (62,63).

Most people with strokes do not need PFO assessment because even though it is present, it is unrelated to the stroke; in these patients, PFO becomes just a confounding factor.

A PFO aetiology should be suspected only when all conventional and the most powerful risk factors for cerebrovascular events have been excluded (cryptogenic strokes). The RoPE point score may be a useful to stratify the risk of stroke related to PFO (42).

A PFO is more likely to be responsible for stroke when combined with other anatomical and clinical factors. A large PFO with long tunnel, a right-to-left shunt already visualised under basal conditions and/or associated with ASA, prominent Eustachian valve, and Chiari network are anatomical criteria identifying a high-risk PFO. Multiple ischaemic lesions detected on CT/MRI, recurrent clinical events, history of deep vein thrombosis or pulmonary embolism, embolic events occurred during/after Valsalva manoeuvre, ischaemic events occurred on awakening in patients with obstructive sleep apnoea syndrome, or associated with immobility or after a long journey, and presence of simultaneous systemic/pulmonary embolism are clinical situations very often associated with PFO (64).

The search for PFO is justified only after a first cryptogenic TIA/stroke. In these cases, the first tool to be performed is TCD, which, if positive for right-to-left shunt, must be followed by cTTE that in most of cases provides accurate information for risk stratification. TEE is useful in all cases in which cTTE is not conclusive, or in preparation for percutaneous closure to fully appreciate the septal anatomy and atrial structures.

Only patients in secondary prevention must be treated. In these cases, according to the current guidelines, antiplatelet treatment is recommended indefinitely. Anticoagulant therapy may be considered as alternative to antiplatelet treatment in patients at high risk of stroke recurrence (62–64).

Only highly selected population at greatest risk can take advantage of percutaneous PFO closure in secondary prevention and may benefit from the closure over a multiple year period (59). Indiscriminate device closure of PFO in patients with cryptogenic stroke/TIA is inappropriate and not indicated (49–53,59).

Conclusion

After many years of interest on PFO, several prospective studies carried out and some randomised trials terminated, but there still remain uncertainties as to whether PFO is a predictor of ischaemic events and which is the best treatment to prevent stroke recurrence. At present, studies suggest a clinical benefit from closure without a definitive answer, and all data from trials indicate careful patient selection in cryptogenic stroke. The future goal will be to improve the ability of patient selection and treatment for individual patients, and for this, we are on good track.

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Author contributions

Doctor Savino conceived and wrote this manuscript. Doctors Savino, Palmiero and Maiello and Professors Pelliccia and Ambrosio have critically discussed, reviewed and approved this article.

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