

Percutaneous closure should be performed in all patients with patent foramen ovale and cryptogenic stroke

Agonist

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The association among intracardiac shunts, cryptogenic stroke and migraine represents an area of investigation that could have significant implications for several patients, and could improve our understanding of such phenomena.

In young adults under 55, the presence of non-embolic ischemic stroke on the left side of the heart presupposes the presence of paradoxical embolism, therefore the presence of patent foramen ovale should be discarded.

However, we must define both situations.

CRYPTOGENIC STROKE

The diagnosis of cryptogenic stroke (CS) is a diagnosis of exclusion. In case of ischemic stroke evaluated by computed tomography (CT) or magnetic resonance imaging (MRI) in young adults, its embolic origin on the left side of the heart should be discarded: a) in the left atrium, in the absence of permanent or paroxysmic arrhythmias like flutter or atrial fibrillation, with no left atrial appendage thrombus, b) in the left ventricle, in the absence of aneurysms or thrombus, c) in the ascending aorta, with no calcifications, d) in the carotid arteries, with no obstructions, and e) in intracerebral vessels. Only then should the presence of patent foramen ovale be investigated with transcranial echo-Doppler or transesophageal echocardiogram with Valsalva maneuver. (1)

PATENT FORAMEN OVALE

All mammals have a patent foramen ovale (PFO). Since the fetus cannot breathe, oxygen is obtained through the placenta. Mammals have evolved a mechanism for passing placental oxygenated blood from the inferior vena cava through the PFO to the left atrium (LA), then to the left ventricle (LV) and the aorta, to finally irrigate the brain.

The PFO is not a hole or empty space such as an atrial septal defect, but a passageway with a flap that allows for the one-way passage between the atriums, from right to left. Post partum, after the lungs expand, the left atrial pressure exceeds the right atrial pressure, pressing the septum primum against the

septum secundum, and right to left shunting ceases. In the majority of people, foramen ovale is closed permanently during the first year of life. However, lack of post natal tissue fusion results in a PFO. This foramen remains patent in about 25% of adults. (2-4)

Although the PFO has been described for centuries, no one believed that it was of any clinical consequence. With the advent of echocardiography, isolated examples of clots that were trapped in the PFO straddling the atrial septum were reported. If these clots –1 to 3 mm diameter– pass to the pulmonary circulation, they produce a pulmonary embolus with no clinical impact; instead, if they pass through the foramen to the brain circulation, they produce a devastating impact.

There are two necessary conditions required for this hypothetical etiology of paradoxical embolism. The first is the presence of a small venous thrombus that can be located in the FO, in the pelvic veins, or in the lower limb venous system. However, it is difficult to diagnose, either through phlebography (only 10%) or MRI (20%). (5, 6) The second necessary condition for paradoxical embolism is a right to left shunting through the PFO. It is possible to diagnose shunting presence in about 70% of the cases through transcranial Doppler with Valsalva maneuver or cough test, or through transesophageal echocardiography with Valsalva maneuver.

The only setting where a paradoxical embolism is considered to be the etiology for stroke is when a young person (under 55-60 years old) with no obvious predisposing risk factors for stroke presents with the sudden onset of neurologic deficit and a CT or MRI pattern diagnosing an isolated recent stroke. (7, 8)

THE DIAGNOSIS OF CRYPTOGENIC STROKE IS A DIAGNOSIS OF EXCLUSION

There must be no other structural abnormalities on the MRI that could account for the neurologic findings. In addition, there must be no other potential causes of embolic phenomena, such as atrial fibrillation, mitral stenosis, or significant atherosclerotic disease of the ascending aorta, carotid or cerebral vessels.

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As part of this evaluation, it is routine to perform a transesophageal echocardiogram with Doppler to evaluate the atrial septum, both at rest with agitated saline injection as well as with Valsalva maneuver or cough test.

A minority of patients –around 5%– report that their stroke occurred shortly after predisposing conditions, such as extended airplane or automobile rides. Another 10% of patients associate the onset of the stroke with physical straining, such as going to the bathroom or lifting a heavy object. Another probable condition is pregnancy, because it predisposes to pelvic venous thrombosis.

All patients with cryptogenic stroke should be evaluated so as to determine whether they have a hypercoagulable state. The most prevalent condition predisposing to this situation is the pharmacologic use of estrogen contained in birth control pills or hormone replacement therapy. The antiphospholipidic syndrome is another condition to be considered. (7)

There are other conditions in which cryptogenic stroke due to paradoxical embolism through PFO can occur, as in the case of the neurological decompression syndrome in divers, and platypnoea-orthodeoxia syndrome.

Neurological decompression illness

It is due to formation of free nitrogen gas bubbles coalescing in the vasculature from tissues as the diver ascends to the surface. (9, 10) Incidence of PFO is increased for patients who develop this type of illness. Cerebral ischemic lesions in divers with PFO are twice those in divers without PFO. Percutaneous closure of PFO has been successful in preventing recurrence of neurological decompression illness in divers. (11)

Platypnea-orthodeoxia

This syndrome is rare and difficult to understand; patients develop dyspnea and arterial unsaturation in the upright position. (12, 13) This condition is caused by the orthostatic stress of a right to left shunting through an atrial septal defect, usually a PFO. This syndrome occurs in patients with severe lung disease, such as pneumonectomy, recurrent pulmonary embolus, or chronic obstructive pulmonary disease. Pulmonary pressures are normal. The pathophysiological mechanism is unknown. Percutaneous closure of PFO or ASD showed an increase of arterial oxygen saturation, and improvement of breathing symptoms. (14)

Treatment

Despite the medical advances in migraine treatment, many patients still suffer frequent and incapacitating episodes. (15)

A 12% of the population (18% women and 6% men) is affected by migraine. Moreover, migraine is a risk factor for stroke occurrence in young patients, particularly in women using oral contraceptives. (16)

The most important epidemiologic study about the relation between cryptogenic stroke, PFO and migraine was published in 2002 by Lamy et al. (16) In 500 patients with cryptogenic stroke, 46% were found to have PFO, and migraine was twice as common among patients with PFO (28%) as it was among those who did not have it (14%). Several studies suggest that the right to left shunt with microemboli can play a significant role in the etiology of migraine. (17) Another hypothesis is that PFO allows for the right-to-left passage of chemicals that could trigger migraine development in susceptible patients. Without PFO, those chemicals would first pass through the lungs, where they could be degraded, diluted, or metabolized. (17)

Several authors have described a reduction or disappearance of migraine in patients whose PFO or ASD closed percutaneously. (18, 19)

Cryptogenic stroke

Percutaneous closure of PFO appears to be a reasonable option for cryptogenic stroke. However, it should be considered that the mere presence of PFO –even with atrial septal aneurysm– has no indication for closure. (19)

In the United States, the FDA has approved the PFO closure for cryptogenic stroke recurrence. However, the defect closure is indicated for the very first stroke. (18)

In our country, opinions vary from one option to the other, depending on the primary care physician's criteria.

Another difficulty to be considered is whether the primary care physician is a clinician, a cardiologist, or a neurologist. In general, both the clinician and the cardiologist usually discard the presence of PFO; on the other hand, neurologists rarely investigate that possibility.

In the case of the first episode of cryptogenic stroke, our position is to explain the patient the different therapeutic alternatives:

- a) Antiplatelet therapy to prevent a second stroke.
- b) Anticoagulant therapy, for the same reason.
- c) Percutaneous closure of PFO.
- d) Surgical closure (although it is not recommended because it is very aggressive).

However, there are situations in which we strongly recommend transcatheter closure:

- a) Recurrent cryptogenic stroke.
- b) Cryptogenic stroke in patients with contraindication to platelet or anticoagulant therapy.
- c) Pulmonary embolism + PFO.
- d) Cryptogenic stroke in patients with hypercoagulability.
- e) Professional deep sea divers + PFO.
- f) Platypnea-orthodeoxia syndrome.
- g) Continuous incapacitating migraines.

Prospective randomized multi-center clinical trials comparing medical therapy to percutaneous clo-

sure of PFO are necessary in order that percutaneous closure of PFO be an absolute indication.

PERCUTANEOUS CLOSURE OF PFO

In our experience, we have performed this procedure on 45 patients aged between 25 and 59 years old (median 42), from October 2002 to April 2009.

Out of these patients, 39 had had cryptogenic stroke, 2 were divers, 2 had platypnea-orthodeoxia syndrome, and 2 suffered migraines; 25 were women and 20 were men. All of them had complete closure, two of them with residual shunt; one patient was implanted a second device, and another one had a relapsing stroke; for this last one, we consider he should be implanted a second occluder.

CONCLUSIONS

1. PFO closure in patients under 55 years old with cryptogenic stroke is an alternative to the traditional therapy (antiplatelets or anticoagulants), and to surgery.
2. In these cases, it is necessary to perform additional exams to prove that the closure by device is an absolute indication.
3. Cryptogenic stroke (CS) or ischemic stroke (IS) + PFO: antiplatelets or closure by device.
4. CS or recurrent IS + PFO: percutaneous closure of PFO.
5. CS or IS + PFO + atrial septal aneurysm (4%): percutaneous closure.
6. CS or IS + PFO + deep vein thrombosis: percutaneous closure.
7. CS or IS + PFO + history of CS: percutaneous closure.

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Declaration of conflict of interests

The author declares he does not have a conflict of interests.

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The illiterate of the 21st century will not be those who cannot read and write, but those who cannot learn, unlearn, and relearn.

A. TOFFLER (1928-)

This controversy (from latin *controversia*. dispute between two or more sides holding opposing views) refers to the prescription of percutaneous closure of patent foramen ovale (PFO) in any patient with cryptogenic stroke (CS) presenting such atrial septum ‘abnormality’ (while the *Real Academia de la Lengua Española* does not accept the term *criptogénico* [cryptogenic], it does accept *críptico* [cryptic]: from Gr. ἐνόδηεῦδ, hidden, enigmatic). The interest in this topic is evidenced when resorting to Pubmed, which includes 154 entries dealing with ‘PFO + CS’ over the last 5 years.

INTRODUCTION

As an introduction, it should be pointed out that the expression ‘*Percutaneous closure should be performed in any patient with PFO and cryptogenic stroke*’ categorically indicates that, from the point of view of the guidelines and medical consensus, a class I recommendation should apply (‘should’, ‘it is recommended’, ‘it has been indicated’, ‘it is useful, or effective, or beneficial’). Such recommendations must be based on the conviction that the therapy benefit (efficacy, tolerability) by far exceeds the eventual risks (side effects, interactions, carcinogenesis, mutagenesis, terata, decreased fertility, effects during pregnancy, overdose, contraindications, etc.). For that, it is necessary to have enough scientific evidence from multiple randomized controlled trials or from meta-analyses, in which multiple population risk strata are evaluated (sex, age, history, etc.), and to have general consistency of direction and magnitude of effect (level of evidence A).

Indication for a procedure may be allowed due to a particular need. In this regard, it is worth mentioning that in December 2001, the use of percutaneous closure devices received approval by the United States Food and Drug Administration (FDA), under humanitarian device exemption, for patients with recurrent cryptogenic stroke due to alleged paradoxical embolism through PFO for whom conventional medical treatment failed. This exemption was cancelled on October 31, 2006; in order to approve the procedure, evidence from clinical trials is required. (1)

Below is a brief exposure of the reasons why I consider that, in the current state of knowledge, the strong recommendation that ‘*Percutaneous closure should be performed in any patient with PFO and cryptogenic stroke*’ does not have enough evidences that justify it.

PATENT FORAMEN OVALE

The foramen ovale is a communication between both atrials, located in the lower part of the atrial septum. It is indispensable for fetal life, and persists in approximately in 30% of the adults. (2) (Figure 1).

CRYPTOGENIC STROKE

The National Institute of Neurologic Disease and Stroke (NINDS) Stroke Data Bank and its modification in the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) define cryptogenic stroke as an infarction which cannot be attributed to a source of definite cardioembolism, large artery atherosclerosis or small artery disease, despite extensive vascular, cardiac, and serologic evaluation. (3)

According to Guerncini et al., the reasons for a stroke to be a cryptogenic stroke include: (4)

1. The cause of stroke may be transient and reversible, and the diagnostic work-out is not therefore performed at the appropriate time. Examples of this situation are the paroxistic atrial fibrillation, transient and reversible vasospasm, and transient embolic arterial occlusion. (4)
2. Causes of stroke are not fully investigated. Table 1 includes a summary of the diagnostic procedures

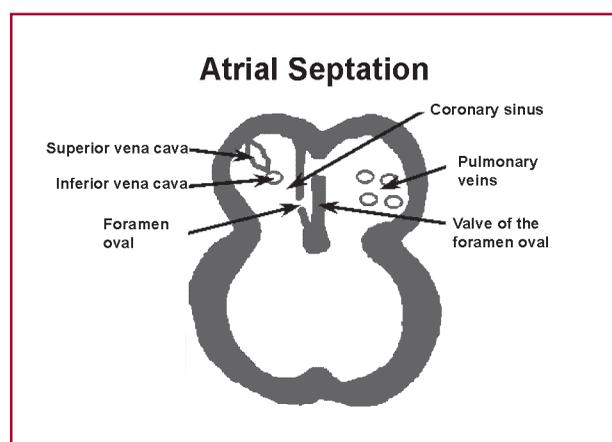


Fig. 1. Atrial septation, according to Marino TA. Development of the cardiovascular system. (Modified with the authorization of: http://isc.temple.edu/marino/embryology/Heart98/heart_text.htm [consulted: May 20, 2008])

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Table 1. Diagnostic procedures for stroke

<p>First level of investigation (50-55%)*</p> <ul style="list-style-type: none"> - Medical history - Risk factors - Neurologic assessment - Lab testing (including erythrocyte sedimentation rate and C-reactive protein) - ECG - Echography and Doppler of extracranial arteries - Brain CT Scan
<p>Second level of investigation (10-15% more)*</p> <ul style="list-style-type: none"> - Transthoracic echocardiogram - Contrast transcranial Doppler - Transesophageal echocardiogram - 24-hour ambulatory ECG (Holter) or 7-day ambulatory ECG monitoring (event-loop recording) - Brain MRI Scan and angio-resonance
<p>Third level of investigation (3-4% more)*</p> <ul style="list-style-type: none"> - Coagulation and autoimmunity assessment (antinuclear antibodies, anti double stranded DNA, anti SM, antiphospholipids, lupus anticoagulants, C-deficient protein, S-deficient protein, or antithrombin deficiency) - Intraarterial angiography - Cerebrospinal fluid analysis - Genetic testing (G1691A mutation of the factor V gene, G20210A prothrombin variant, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke), Fabry disease, and collagen vascular disease) - Skin biopsy, and skeletal muscle biopsy <p>*Percentages represent the likelihood of finding stroke etiology with each level of investigation.</p>

Reproduced with the authorization of Guercini F, Acciarresi M, Agnelli G, Paciaroni M. Cryptogenic stroke: time to determine aetiology. *J Thromb Haemost* 2008; 6:549-54.

for stroke. According to the authors, a 24-hour ambulatory ECG or a 7-day ambulatory ECG monitoring (event-loop recording), a contrast transcranial Doppler, and a transesophageal echocardiogram should be performed to reduce the percentage of stroke of unknown etiology. (4)

The cryptogenic stroke category includes strokes associated with potential causes of cardiac embolism, like patent foramen ovale (PFO) with or without atrial septal aneurysm (ASA), aortic arch atheroma, mitral valve stands, strokes associated with antiphospholipid antibodies, and strokes with two or more equally plausible etiologies. Cryptogenic strokes stand for 30-40% of ischemic strokes. (2) From the physiopathological point of view, cryptogenic stroke would be associated to paradoxical embolism secondary to PFO or other

abnormalities of the atrial septum, occult embolism secondary to atheromatous disease, occult paroxysmal atrial fibrillation or other cardiac embolic sources, thrombophilia (antiphospholipid antibodies or neoplasias), preclinical or subclinical (intracranial or extracranial) cerebrovascular disease, or inflammatory processes (C-reactive protein or chronic infections). Stroke recurrence rate is 1.6% at one week, 3-4.2% at one month, 5.6% at three months, 14-20% at two years, and about 33% at five years. (2)

RELATION BETWEEN PATENT FORAMEN OVALE AND CRYPTOGENIC STROKE

The causal relation (Arthur B. Hill's causality criteria: strength of association, dose-response effect or gradient, temporal sequence, consistency, coherence, analogy, biological plausibility, specificity, experimental evidence) between PFO and stroke is controversial. Indeed, in 2000 Overell et al. published a meta-analysis in which they state that PFO is associated significantly with stroke in patients under 55, and they warn that more studies are required to determine if there is association between PFO and stroke in patients over 55. (5) Recently, Alsheikh-Ali et al. conducted a systematic review of 23 case-control studies that examined PFO prevalence in patients with cryptogenic stroke versus control subjects with stroke of known cause. These authors conclude that about one third of the PFO found in patients with cryptogenic stroke are just incidental (accessory, of little importance). (6) The American Academy of Neurology (AAN) considers that PFO is not associated with significantly increased risk of recurrent stroke after cryptogenic stroke, and that the combination of PFO and ASA may increase the risk of recurrent stroke in patients under 55 years of age with cryptogenic stroke. (2)

It should be pointed out that in patients with cryptogenic stroke and PFO, with or without ASA, it is rare (10-22%) to find the embolic source in the lower limb veins. This is because the platelet embolus is too small to be targeted by conventional methods, the thrombus is formed in the borders of the PFO or the ASA, or the embolic source is systemic (arterial). (2)

SECONDARY PREVENTION IN PATIENT WITH CRYPTOGENIC STROKE AND PATENT FORAMEN OVALE

Therapeutic options for secondary prevention of embolic stroke in patients with cryptogenic stroke associated to PFO, ASA, or both, include medical antiplatelet or anticoagulant therapy, and surgical or percutaneous closure of the defect. Below are the relevant reviewed evidences available in literature:

1. The study of the Patent Foramen Ovale and Atrial Septal Aneurysm Study Group showed that, of all cryptogenic stroke patients treated with aspirin

- 300 mg/day, 2.3% patients with isolated PFO, 15.2% with PFO and ASA, and 4.2% without PFO or ASA presented stroke recurrence at four years. (7)
2. The PFO in Cryptogenic Stroke Study (PICSS) verified that, of all cryptogenic stroke patients treated with aspirin or warfarin, recurrence of stroke at 2 year follow-up was similar in patients with PFO (14.8%) compared to those without PFO (15.4%), with small PFO (18.5%) or large PFO (9.5%), in patients with isolated PFO (14.5%) or associated to ASA (15.9%), and in patients treated with warfarin (16.5%) or aspirin (13.2%). (8)
 3. In a review on stroke patients with PFO who underwent surgical closure of the defect, Dearani et al. observed stroke recurrence in 7% of the patients at 1 year, and in 17% of the patients at 4 years. (9)
 4. In 28 cryptogenic stroke patients with PFO who underwent surgical closure of the defect, Homma et al. observed recurrence in 4 patients (19.5% at 13 month-follow up) exclusively over 45 years old. The authors concluded that despite PFO can be easily repaired in cryptogenic stroke patients, it does not prevent recurrence of ischemic events consistently; this would be more frequent in older patients. (10)
 5. **Khairy** et al. conducted a systematic review of secondary prevention of cryptogenic stroke in all the publications in English with more than 10 patients and with a follow-up of at least 1 year. The authors included 10 studies with percutaneous closure of PFO (1,355 patients) and 6 studies with medical treatment (895 patients). The annual incidence of recurrent stroke was 0-4.9% for patients treated with percutaneous closure, and the incidence of major complications (death, bleeding requiring transfusions, cardiac tamponade, need for surgery, fatal massive pulmonary embolism) and minor complications (bleeding with no transfusion requirement, periprocedural atrial arrhythmias, transient atrioventricular block, device arm fracture, device embolization with catheter retrieval, asymptomatic thrombosis of the device, need for new catheterism, symptomatic air embolism, transient ST segment elevation, AV fistula, femoral hematoma) was 1.5% and 7.9%, respectively. Annual incidence of recurrent stroke was 3.8-12.0% in patients medically treated (antiplatelets and/or anticoagulants). The authors point out that the superiority of any of the therapies cannot be inferred because data are not controlled and definitions are standardized, and that there is no balance among the basal characteristics of patients (patients treated with percutaneous closure of PFO had higher recurrent strokes, whereas those medically treated were older, were mostly men, and had more prevalence of diabetes and smoking). In their conclusions, the authors highlight the need for controlled and randomized clinical trials. (11)
 6. In a retrospective study, Windecker et al. report that cryptogenic stroke patients with PFO treated with percutaneous closure of PFO, and with a 4-year follow up, had less combined events (death, stroke, and transient stroke) than those who received antiplatelet therapy (8.5% versus 28.3%; $p = 0.03$), but had a similar number of events compared to those patients under anticoagulant therapy (8.5% versus 13.3%; $p = 0.32$). Patients with more than one stroke and complete closure of PFO had less recurrent strokes and transient strokes than those receiving antiplatelets (6.5% versus 42.6%; $p = 0.005$), but had a similar number compared to those patients under anticoagulant therapy (6.5% versus 17.9%; $p = 0.18$). (12)
 7. Braun et al. reported an annual incidence of recurrent stroke of 0.6%, transient stroke of 0%, and peripheral embolism of 0.2%, after percutaneous closure of PFO in cryptogenic stroke patients. The rate of complications was 0.24% (ST segment elevation, AV fistula, transient stroke, device displacement). (13)
 8. Spies et al. studied 403 patients who were performed percutaneous closure of PFO. Before closure, annual incidence of cryptogenic stroke was 3.1%, and incidence following closure was 2.0%. The rate of complications was 2.0% for the procedure, 10.8% for residual shunt, 0.02% for transient thrombosis in device, and 0.03% for cable fracture. (14)
 9. At present, there are eight clinical trials registered in ClinicalTrials.gov (registry of clinical trials of the United States National Institutes of Health and the Food and Drug Administration) (Table 2). Two of them were completed, one was suspended, and five are in progress. (15)

CONCLUSIONS

In my opinion, there is not relevant scientific evidence from controlled and randomized trials or meta-analyses in which multiple population risk strata are evaluated, and in which there is general consistency of direction and magnitude of effect (level of evidence A) that justify the imperative recommendation that “*Percutaneous closure should be performed in any patient with PFO and cryptogenic stroke*” (class I recommendation). This recommendation would reach level II only. It still has to be defined whether the benefit exceeds the risk (for which additional studies with focused objectives are needed); it would then be reasonable to perform the procedure (class IIa). If the benefit exceeds the risk marginally or is similar to the risk (for which additional studies with broad objectives and/or registry data are needed), therefore it could be considered only as a therapeutic option (class IIb). At present, when dealing with an individual patient with cryptogenic stroke and PFO, only a sensible assessment of the clinical situation, the patient’s preferences, and the evidence available –which is unfortunately insufficient– are possible.

Table 2. Clinical trials registered in ClinicalTrials.gov (clinical trials registry of the U.S. National Institutes of Health and the Food and Drug Administration)

Study	Condition	Intervention	Phase	Status
Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS)	Ischemic stroke Patent foramen ovale	Drug: Warfarin Drug: Aspirin	IV	Completed
Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE)	Ischemic stroke Patent foramen ovale Interatrial septum aneurysm Migraine	Drug: Aspirin Drug: Anti-vitamin K Device: Patent foramen ovale closure devices	III	Recruiting patients
Evaluation of the STARFlex™ Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale	Patent foramen ovale Ischemic stroke / Ischemic TIA	Device: STARFlex™ Septal Closure System Drug: The best medical treatment	II-III	Active, not recruiting patients
PC-Trial: Patent Foramen Ovale and Cryptogenic Embolism	Paradoxical embolism, interatrial septum defects	Device: Percutaneous closure of patent foramen ovale	IV	Recruiting patients
The Swiss Patent Foramen Ovale Consortium	Ischemic stroke / Ischemic TIA	Drug: Antithrombotic therapy Device: Percutaneous device of patent foramen ovale		Recruiting patients
GORE HELEX™ Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients (Gore REDUCE)	Ischemic stroke / Ischemic TIA	Device: GORE HELEX™ septal occluder	III	Enrolling participants by invitation only
PfX Closure System in Subjects With Cryptogenic Stroke, Transient Ischemic Attack, Migraine or Decompression Illness (Patent Foramen Ovale)	Patent foramen ovale	Device: PfX catheter		Suspended
The Paradigm II Trial: PFX Closure System in Subjects With Cryptogenic Stroke, Transient Ischemic Attack, Migraine or Decompression Illness	Patent foramen ovale	Device: PFX closure system		Completed

Modified from: <http://www.clinicaltrials.gov> [consulted: May 20, 2009].

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Declaration of conflict of interests

The author declares he does not have a conflict of interests.

AGONIST'S REPLY

I agree with my antagonist in that the title of the controversy, "*Percutaneous closure should be performed in all patients with patent foramen ovale and cryptogenic stroke*", is a statement that has not been yet supported with evidence from controlled clinical trials. However, based on the literature and on my personal experience, I consider that the benefit exceeds the risk.

Nevertheless, as Dr. Piñeiro argues, the patient should be clinically and individually evaluated, and should be presented the different alternatives, with their benefits and risks, as well as being made aware of the lack of sufficient evidence for an agreed treatment.

However, PFO –if present– must be closed percutaneously in case of recurrent cryptogenic stroke, and despite the antiplatelet or anticoagulant therapy.

I do not hesitate to recommend percutaneous closure for cryptogenic stroke patients with PFO associated to atrial septal aneurysm, because the risk of stroke recurrence increases significantly.

The same applies in cases of platipnea-orthodeoxia syndrome, since PFO closure is the only effective therapy.

However, evidence is not enough for migraine, and we have to evaluate the patient individually, who often chooses PFO closure after many unsuccessful therapies.

I believe we must watch for the different clinical trials in progress, which will give us a definitive answer to our questions.

Dr. Horacio J. Faella^{MD}

ANTAGONIST'S REPLY

I am glad to agree with Dr. Horacio Faella on the basics of this issue: "*Prospective randomized multi-center clinical trials comparing medical therapy to percutaneous closure of PFO are necessary*" (HJF). In the meantime, at present only a sensible assessment of the clinical situation, the patient's preferences, and the evidence available –which is unfortunately insufficient– are possible.

However, it is convenient to resort to the available recommendations in order to guide therapeutic decisions. In this regard, I believe that the guidelines from *Société Française Neuro-Vasculaire* (Albucher JF, Chaine P, Mas JL, Moulin T, Rodier G, Cohen A, et al. *Consensus sur les indications de la fermeture endovasculaire du foramen ovale perméable après un accident ischémique cerebral*. *Rev Neurol (Paris)* 2007;163:1127-9.) are extremely reasonable:

- Endovascular PFO closure is not recommended for patients with a first cryptogenic stroke associated to isolated PFO (with no ASA), since, in the trials available, these patients are not at higher risk of relapse compared to patients who have cryptogenic stroke not associated to PFO.
- For patients under 55, endovascular PFO closure could be considered in the following cases:
 - PFO with or without ASA and relapsing cryptogenic stroke under well conducted anticoagulant therapy or when it is contraindicated.
 - PFO with or without ASA and venous thromboembolic disease with high risk of relapsing thrombosis.
 - PFO with ASA, and patient's refusal to anticoagulant therapy.
- When endovascular PFO closure is considered, the patient must be provided with the following information:
 - The presence of isolated PFO is not associated to an increase in the risk of relapsing.
 - The presence of PFO and ASA seems to be associated to higher risk of relapsing in patients under 55 years of age.
 - PFO closure should be considered only after stroke relapsing under well conducted anticoagulant therapy.
 - No study has demonstrated that this treatment is more effective than antiplatelet or anticoagulant therapy.
 - Performing this treatment does not ensure that the patient will not have a new stroke.

- PFO closure does not free the patient from long term antiplatelet therapy.
- The patient must be made aware of the possible complications of this treatment.
- Cryptogenic stroke diagnosis must be confirmed within a “neurovascular setting”.
- PFO with or without ASA must be diagnosed with certainty by an experienced team.
- PFO closure with interventional catheterization should be performed in a cath lab close to a cardiac surgery center, by a physician trained in interventional catheterization techniques, especially in crossing the interatrial septum. This is a procedure that is not performed as an urgency when stroke is indicated. Catheterization is performed

under infective endocarditis prophylaxis and with heparin. PFO closure is associated to long term antiplatelet therapy.

- Patient’s follow up after PFO closure must be multidisciplinary, and must include a neurologist and a cardiologist.

To sum up, I believe that while **“percutaneous closure should be performed in any patient with PFO and cryptogenic stroke”**, it should be pointed out that **“percutaneous closure can be considered only for certain patients with PFO and cryptogenic stroke”**.

Dr. Daniel J. Piñeiro^{MD}