[Expert opinion paper]

Management of patent foramen ovale in cryptogenic stroke

Werner BUDTS[1], MD, PhD; Victor LEGRAND[2], MD, PhD; André PEETERS[3], MD; Vincent THIJS[4], MD, PhD

[1]Dept. of Cardiology, Universitaire Ziekenhuizen Leuven, Leuven; [2]Dept. of Cardiology, Centre Hospitalier Universitaire, Liège; [3]Dept. of Neurology, Université Catholique de Louvain, Brussels; [4]Dept. of Neurology, Universitaire Ziekenhuizen Leuven, Leuven, Belgium & Laboratory of Neurobiology, Vesalius Research Center, VIB, Leuven, Belgium.

Paper endorsed by the Belgian Society of Cardiology; document reviewers: Patrick Evrard, Georges Mairesse, Marielle Morissens, Guy Van Camp, Philippe Van de Borne, Frank Van den Branden.
Paper endorsed by the Belgian Stroke Council; document reviewers: Raf Brouns, Patrick Cras, Peter Paul De Deyn, Sylvie Deraedt, Philippe Desfontaines, Aloys Dewindt, Dimitri Hemelsoet, Robin Lemmens, Patricia Redondo, Matthieu Rutgers, Rishi Sheorajpanday, Yves Vandermeeren, Peter Vanacker, Geert Vanhooren, William Van Landeghem.

Abstract There is currently no consensus on the optimal management of cryptogenic stroke in the presence of a patent foramen ovale (PFO). Some physicians do not believe in the added value of PFO closure in cryptogenic stroke, whereas, for others, cryptogenic stroke represents a situation where PFO closure would be the best management. Because of a lack of well-designed randomized trials, guidelines do not provide a clear answer. Therefore, the cardiological and neurovascular societies in Belgium decided to write an attempt at an expert opinion paper.

Keywords *Expert opinion – patent foramen ovale – stroke – cryptogenic – closure.*

INTRODUCTION

Today, there is no consensus on the optimal management of cryptogenic stroke in the presence of a patent foramen ovale (PFO). Because of a lack of well-designed randomized trials, guidelines do not provide a clear answer. Some physicians do not believe in the added value of PFO closure in cryptogenic stroke, whereas, for others, cryptogenic stroke represents a situation where PFO closure would be the best management[1]. Today, the variety of expert opinions makes it difficult for the practitioner to make a choice. In November 2010, the results of the Closure I randomized controlled clinical trial were presented in Chicago during the American Heart Association congress. In this trial, PFO closure was not superior to the best medical treatment to prevent stroke recurrence. Moreover, the incidence of adverse events in the PFO closure group was quite high, questioning the safety of the closing procedure. Because of these findings, physicians are more reluctant to choose PFO closure in patients with stroke. Therefore, the cardiological and neurovascular societies in Belgium decided to write an expert opinion paper. The paper reviews the limitations of the current evidence and aims to act as a guide in the management of patients with PFO. It is not a comprehensive review of the literature but reflects the opinion of a panel consisting of cardiologists and neurologists who are involved in the treatment of stroke and the performance of PFO closure.

Address for correspondence:

Werner Budts, MD, PhD, Dept. of Cardiology, Universitair Ziekenhuis Leuven, Herestraat 49, B-3000 Leuven, Belgium.
E-mail: werner.budts@uz.kuleuven.ac.be

Received 16 November 2011; accepted for publication 22 November 2011.

ANATOMY OF THE INTERATRIAL SEPTUM

The interatrial septum is located between the left and right atrium and consists of two parts: the septum primum and the septum secundum[2]. Although the septum secundum is in general the thicker part of the interatrial septum, it does not completely separate both atria. A residual communication persists between the left and right atrium, which is covered on the left side of the septum by the thinner septum primum. The anatomical position of both parts of the interatrial septum allows

the septum primum to function as a valve with mainly right to left shunting. This opening is called the foramen ovale (FO) (figure, panel A). Before birth, a part of the oxygenated blood coming from the umbilical vein is immediately redirected from the right atrium through the FO into the left atrium and systemic circulation, bypassing the -at that time- non-functional lungs. The Eustachian valve, which originates from the ostium of the inferior vena cava, creates a sort of canal and favours the bloodstream from the inferior vena cava to the interatrial septum. After birth, when the pressures in the right heart circulation drop and the lungs deploy by the first breath, the pressure difference between left and right atrium rises, pushes the septum primum on the septum secundum, and functionally closes the FO. Later, in three quarters of the population, the FO closes also anatomically. However, in the remaining part, the foramen remains patent, is then called PFO, and allows right to left shunting. The overlap between septum primum and septum secundum is frequently called 'the tunnel' (figure, panel A). This tunnel can be widely opened by a Valsalva manoeuvre, by a diameter of up to two centimeters or more.

Sometimes, the interatrial septum makes an excursion to the left, to the right, or to both atria, at each heart beat, the so-called mobile interatrial septum. Depending on the definition, when the excursion of the interatrial septum exceeds ten millimeters, the septum is determined as an atrial septal aneurysm (ASA)[3,4] (figure, panel B). A mobile interatrial septum (or an ASA) can be present with or without PFO.

A PFO is frequently confused with atrial septal defect (ASD). PFO has no tissue defect, whereas an ASD is missing tissue by definition. When tissue of the septum primum is deficient, the defect is called the ASD secundum type (figure, panel C); when tissue of the septum secundum is deficient, the defect is called the ASD septum primum[5]. In general, a left-to-right shunt, which leads to volume overload of the right heart, mainly characterizes ASDs. However, because of pressure differences between both atria, intermittent right-to-left shunting is not unusual.

DETECTION OF RIGHT-TO-LEFT SHUNT

Several techniques are able to detect a right-to-left shunt. Contrast transthoracic echocardiography is one way to look for shunting. Agitated saline or an equivalent is injected in a brachial vein and the intra-cardiac course of the contrast is observed. When the contrast appears in the left atrium with or without a Valsalva manoeuvre, the diagnosis of a right-to-left shunt is made[6]. However, it is difficult for the sonographer to differentiate between a right-to-left shunt through a PFO and other sources of shunting, such as pulmonary arterio-venous malformations (lung fistula). The time frame in which the contrast appears in the left atrium after injection in a brachial vein, might favour the diagnosis of an intra- or extracardiac (intrapulmonary) shunt.

Another possibility to detect right-to-left shunt is the use of a transcranial Doppler[7]. The diagnostic principle is the same as with contrast transthoracic echocardiography. Contrast is injected in a brachial vein and detected by Doppler in the cranial arteries. The sensitivity to detect a right-to-left shunt is higher than with transthoracic echocardiography, but the specificity is substantially lower. Indeed, because the heart is not directly

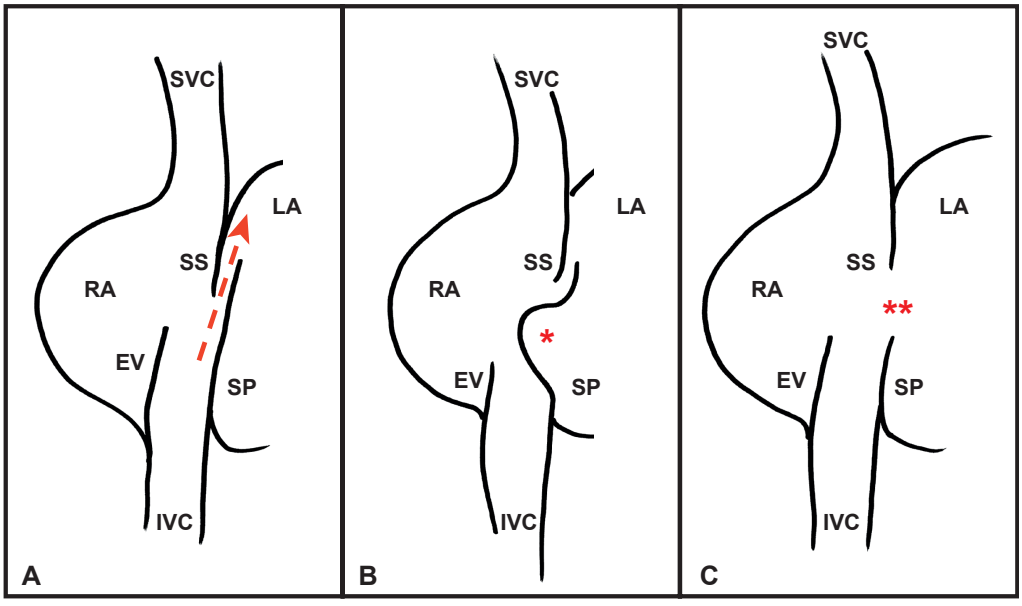

Figure
Panel A: schematic drawing of a patent foramen ovale (dotted red arrow).
Panel B: schematic drawing of an atrial septal aneurysm (*).
Panel C: schematic drawing of atrial septal defect, secundum type (**).
EV: Eustachian valve, IVC: inferior vena cava, LA: left atrium, RA: right atrium, SP: septum primum, SS: septum secundum, SVC: superior vena cava.

visualized by transcranial Doppler, exact determination of the shunt location is not possible. However, the technique might be useful in the screening and even semi-quantification for right-to-left shunt as Valsalva manoeuvres can be performed more accurately.

Finally, a right-to-left shunt through a PFO might also be depicted by contrast transoesophageal echocardiography[8]. The characteristics of the interatrial septum are evaluated under direct two-dimensional or three-dimensional view. Contrast passage between the septum primum and septum secundum, with or without a Valsalva manoeuvre, is pathognomonic of a PFO. The degree of the right-to-left shunt can be semi-quantified by counting the number of bubbles in the left atrium. However, the key point here is the quality of the Valsalva manoeuvre, which is sometimes difficult to perform with a probe in the oesophagus. Indeed, only by reversing the pressure gradient over the interatrial septum, bubbles will pass the PFO from right to left. An insufficient Valsalva manoeuvre will lead to a false negative study. The length of the tunnel between septum primum and septum secundum can be measured, as well as the degree of the excursion of the septum by each heartbeat to determine the septum as mobile or complying with the definition of an ASA. Finally, the length of the Eustachian valve can be estimated. The transoesophageal echocardiogram is mandatory in detecting and localizing a right-to-left shunt. Moreover, in the workup of a cryptogenic stroke, transoesophageal echocardiography is needed to exclude other sources of stroke: intracavitary thrombi, low flow velocities in the left atrial appendage, endocarditis, intracardiac masses, aortic atherosclerosis, etc.

Several centres combine more of these diagnostic examinations in the workup of a cryptogenic stroke patient.

RIGHT-TO-LEFT SHUNT, CRYPTOGENIC STROKE, AND PATENT FORAMEN OVALE CLOSURE

About one decade ago, it was observed that the prevalence of a right-to-left shunt, mainly attributed to the presence of a PFO, was substantially higher in cryptogenic stroke patients than in the general population[9,10]. The hypothesis was generated that paradoxical thromboembolism through a PFO could provoke an unexplained stroke. Several case reports documented thrombi trapped within a PFO, providing direct evidence that paradoxical embolism does exist. In most cases of cryptogenic stroke this direct evidence of thrombi entrapment is lacking, or even more, the proximal source of embolism like a deep venous thrombosis or pelvic vein thrombus goes undetected. Therefore, direct proof of paradoxical embolism is lacking. A causal relationship between cryptogenic stroke and most right-to-left shunts (through a PFO) has not been proven according to strict scientific criteria. This would require a reduction in stroke incidence in the context of a randomized trial.

Given the inherent difficulties in diagnosing paradoxical embolism, a probabilistic and pragmatic approach is often adopted. First, one determines whether other reasons for stroke in younger age patients have been excluded. Specifically, occurrence of paroxysmal atrial fibrillation is often unrecognized on 24-hour Holter ECG. Extending Holter monitoring to 48 or 72 hours is shown to increase the sensitivity to detect paroxysmal atrial fibrillation and should be recommended[11]. For this reason, some people even suggest to implant a loop recorder in the workup of a cryptogenic stroke. However, the yield of long-term recording in patients below 55 years has not been determined since the frequency of atrial fibrillation is low in that age category. Furthermore, the cardiovascular risk profile is examined. If the stroke remains unexplained and the cardiovascular risk profile is low, the likelihood that the PFO is not incidental increases[12]. In this context, we propose to define patients with a low cardiovascular risk profile as patients with a SCORE risk below 5%. A pragmatic definition of cryptogenic stroke is shown in table 1. Table 2 shows the diagnostic approach to stroke in the young. Given the difficulty of reliably diagnosing TIA in the absence of confirmatory tests (table 3), especially in the younger age population where migraine auras and focal seizures are frequent, we propose to consider the PFO to be pathogenic only in patients with short-lasting symptoms in the presence of acute ischaemic lesions on magnetic resonance imaging. If these conditions are fulfilled (unexplained stroke after thorough diagnostic testing in the context of a low cardiovascular risk profile) PFO closure might be considered as a therapeutic option.

PFO CLOSURE

Several studies (retrospective, prospective non-randomized, meta-analyses) have reported that percutaneous PFO closure might be beneficial in preventing recurrence of stroke[13-16]. Some authors have suggested that the degree of the right-to-left shunt, the presence of an atrial septum aneurysm, a long tunnel between septum primum and septum secundum, younger age (preferably younger than, but not limited to 55 years), or a more prominent Eustachian valve were related to a higher recurrence rate of stroke, and therefore represented a good indication for closure[17,18]. Unfortunately, these suggestions were never

Table 1 Diagnostic criteria of cryptogenic stroke

– Neurological symptoms related to cerebrovascular damage (with no limit on the duration of symptoms, even lasting less than 24 hours)
– Single or multiple cerebral ischaemic lesions on magnetic resonance ▫ When multiple brain lesions: ▪ Acute lesions on DWI: exclusion of thrombophilia, endocarditis/cardiac myxoma, cerebral vasculitis, neuroborreliose, syphilis, etc. ▪ Chronic lesions: exclusion of white matter lesions which are mostly an accumulation of the standard cardiovascular risk factors; exclude Fabry's disease, antiphospholipid syndrome, CADASIL, multiple sclerosis, etc.
– No significant lesions in the intra- and extra-cranial arteries which perfuse the targeted region
– No significant other source of cardio-embolism or major aortic atherosclerosis (SCORE risk less than 5%), exclusion of atheroma plaques with a diameter ≥ 4 mm, exclusion of intracavitary thrombus or regional left ventricular hypo- or akinesia in patients with a history of myocardial infarction, exclusion of cardiomyopathies, exclusion of atrial fibrillation
– No haematological disorders, exclusion of extreme anaemia (sickle cell anaemia), polycythaemia vera, thrombocytosis, paraproteinaemia, paroxysmal nocturnal haemoglobinuria
– No oncological disorders
– No inflammatory or connective tissue disease
– No toxicological sources, exclusion of cocaine abuse
– No hereditary disorders, exclusion of MELAS and CADASIL
– Exclusion of typical lacunar infarction (maximal diameter of 15 mm, in basal ganglia, pons, thalamus, capsula interna)
– Exclude combinations of lowered prot C, S, antitrombine, the presence of aPC resistence and PT20210 GA mutation

Table 2 Technical investigations for the diagnosis of cryptogenic stroke

– Magnetic resonance of the brain (or computer tomography scan when magnetic resonance is contra-indicated)
– Duplex of the extracranial arteries
– Contrast magnetic resonance angiography of the cranial arteries with T1 images of the vessel wall or computer tomography angiography (age < 55 years)
– Transthoracic and transoesophageal echocardiography
– 24-h Holter registration or telemetry during observation; if indicated extended Holter monitoring for 47 to 72 hours
– Chest X-ray
– Laboratory screening to exclude: thrombophilia, inflammatory disease, rheumatic disease, lupus, etc.
– Lumbar punction with cerebrospinal fluid analysis (< 55 years or when indicated)
– Evoked potentials if indicated

Table 3 Definition of transient ischaemic attack (TIA)

– TIA is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction
– In young patients, migraine with aura and focal epilepsy should be considered in the differential diagnosis of TIA. Episode(s) of isolated recurrent vertigo in the absence of high-grade vertebrobasilar stenosis is (are) unlikely to be TIA
– Recurrent stereotypic TIA are unlikely to be associated with cardioembolic TIA in the context of PFO
– In the context of young patients with presumed TIA, early (< 72 hours) neuroimaging with DWI and ADC mapping is used to exclude the presence of brain infarction
– The presence of white matter hyperintensities are not sufficient evidence of the presence of brain infarction

Table 4 Expert opinion to close the patent foramen ovale

Reasonable indication for closure:
– Typical cryptogenic brain embolism in young patients with low cardiovascular risk profile (SCORE risk below 5%)
– Non-cryptogenic stroke attributed to paradoxical event (related to deep venous thrombosis, lung embolism, proven passage of thrombus through the patent foramen, etc.)
– Recurrence of typical cryptogenic stroke in patients with low cardiovascular risk profile, already under effective antiplatelet therapy
Grey area:
– Recurrence of typical cryptogenic stroke in patients with high cardiovascular risk profile, already under effective antiplatelet therapy
– Recurrence of transient ischaemic attack in patients with low cardiovascular risk profile, already under effective antiplatelet therapy
Probably no indication for closure:
– Typical cryptogenic stroke in patients with high cardiovascular risk profile
– Transient ischaemic attack
– All non-cryptogenic strokes attributed to a non-paradoxical event

further investigated in methodologically well-designed and sufficiently powered studies. Also, the only randomized controlled clinical trial (Closure I, A Prospective, Multicenter, Randomized Controlled Trial to Evaluate the Safety and Efficacy of the STARFlex Septal Closure System Versus Best Medical Therapy in Patients with a Stroke or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale)[19] failed to show a clinical benefit of PFO closure on top of best medical treatment. The negative results of Closure I, recently presented at the American Heart Association congress (November, Chicago, USA), disappointed a lot of clinicians who initially believed in percutaneous PFO closure. Other studies are still recruiting patients in a randomized setting to demonstrate that PFO closure is superior to best medical treatment (REDUCE, Gore, Flagstaff, AZ, USA; RESPECT, PC trial[20], AGA Medical, Plymouth, MN, USA). Until now, the US Food and Drug Administration approved no device for PFO closure and the scientific societies are waiting for the results of ongoing trials[21,22].

In summary, only after an extensive workup, jointly by a neurologist and a cardiologist, a PFO might be considered as highly pathogenic and considered a potential indication for closure. Moreover, PFO closure is preferentially performed in experienced centres in order to minimize the potential risks. Serious complications, such as device dislocation or peri-procedural wall perforation, have been described infrequently. Table 4 summarizes the indications for PFO closure as suggested by the contributors of this expert opinion and offers more details for closure selection when compared with the AHA/ASA guidelines which state that 'insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy (class IIb, level of evidence C)'[23].

RIGHT-TO-LEFT SHUNT, OTHER PARADOXICAL EVENTS, AND PFO CLOSURE

A right-to-left shunt is not only related to cryptogenic stroke, but also to other paradoxical thrombo-embolic events. Paradoxical emboli through a PFO (or another right-to-left shunt) might also block coronary, central, and peripheral arteries, leading to cardiovascular events. A PFO is frequently closed for this reason, but here also, evidence-based data are lacking. However, when the same train of thought is used as for cryptogenic stroke, patients who are likely to benefit the most from PFO closure will be those with a low cardiovascular risk profile (less than 5% on the SCORE table). Sometimes, therapy with oral anticoagulants is switched to PFO closure combined with antiplatelet therapy, when the use of oral anticoagulants is not tolerated. However, this is an experience-based decision: randomized controlled data on this topic are not available.

In divers, PFO and right-to-left shunt seem also related to a higher number of brain lesions. It is hypothesized that during the ascent, nitrogen bubbles are formed, especially within the venous circulation, which are able to pass through the PFO, and embolize into the cerebral arterial circulation. The discussion whether a PFO needs to be closed in divers as a prevention measure is still ongoing. Although there are no evidence-based data, some insurance companies request PFO closure. It is suggested that when a diver with a PFO suffers from decompression illness, the disease will present more severely[24]. Therefore, especially for professional divers, the stance of the insurance companies to close the PFO, can be understood. Today, PFO closure is only reimbursed in Belgium for patients who suffered from decompression illness but not as a precautionary measure.

In some rare cases, as in patients who underwent unilateral pneumectomy, a PFO is responsible for symptomatic systemic desaturation. Particularly when the patients sit up, a huge right-to-left shunt through the PFO might occur (platypnoea syndrome). This is not treatable by medication and is a clear indication for percutaneous PFO closure[25].

Finally, right-to-left shunt also seems to be related to migraine with aura[26]. It was observed that the number of migraine attacks decreased or that migraine even disappeared in patients who underwent PFO closure after stroke[27]. Several investigators confirmed this finding by retrospective analysis. Also prospective non-randomized trials suggest an effect of PFO closure on the occurrence of migraine with aura. Unfortunately, one prospective randomized controlled trial, MIST, did not show any benefit of PFO closure on the prevalence of migraine[28]. Only a post hoc analysis documented a significant lower number of migraine days. Therefore, it is still too early to consider PFO closure as a treatment for migraine. Trials are ongoing to include patients (PREMIUM, PRIMA, Aga Medical, Plymouth, MN, USA) and results will be known in the next years[29].

TREATMENT AFTER PATENT FORAMEN OVALE CLOSURE

The treatment after PFO closure focuses on two main topics. First, the endothelialization process after device implantation should be optimized. Although there is no strict post-procedural protocol, most centres combine aspirin (at least 80 mg/d) and clopidogrel (at least

75 mg/d) for 4 to 6 weeks. Aspirin has to be continued for at least six months, to ensure complete endothelialization. During these first six months after device implantation, endocarditis prophylaxis is mandatory.

Secondly, secondary cardiovascular prevention has to be taken into account. No one can be sure that a cryptogenic stroke is completely attributable to the PFO and the right-to-left shunt. Indeed, there are still patients who suffer from cryptogenic stroke without PFO and right-to-left shunt. Therefore, continuation of antiplatelet therapy (aspirin or clopidogrel) should be considered. Moreover, all cardiovascular risk factors, if present, need to be treated to recommended targets (blood pressure control, cholesterol lowering, stop smoking, glycaemia control, increase of physical activities, etc.).

Thirdly, regular evaluation of cardiac rhythm to exclude occurrence of atrial fibrillation should be recommended as this arrhythmia might have gone unrecognized before PFO closure or could be triggered by the implant. Should atrial fibrillation occur, oral anticoagulation must be considered instead of antiplatelet therapy[30].

RESIDUAL SHUNTING AFTER PFO CLOSURE AND RECURRENCE OF EVENTS

In most centres, the presence of residual shunting is tested six to twelve months after PFO closure. Indeed, several reports in the literature suggest that recurrence of stroke is related to residual right-to-left shunting[15,31], whereas others do not confirm this finding[32]. There are no clear recommendations about the management of a residual shunt. Probably, there are two types of residual shunting. First, a shunt might persist between both discs and both umbrellas of the device. The maximum diameter of the communication between the atria after device implantation is usually only a few millimeters. Probably this small opening does not pose a significant risk for recurrence of paradoxical embolism. An attempt to close this residual defect is technically challenging and, sometimes, even dangerous. In some patients, the device is wrongly implanted in a fenestration of the interatrial septum (very small atrial septal defect) and not in the PFO. In these selected cases a repeat procedure is useful, feasible, and associated with low complication rates. Probably the latter is the main reason for reoccurrence of stroke. However, when a stroke reoccurs in patients with residual shunting after PFO closure, a new workup, as mentioned earlier, will be mandatory. One should attempt to select devices with the highest closing rates when performing device implantation for PFO closure.

CONCLUSIONS

There is currently no clear evidence that PFO closure is warranted in patients with cryptogenic stroke. PFO closure might be potentially indicated in patients with a low cardiovascular risk profile (SCORE risk below 5%) and in whom all other potential causes of stroke are excluded. This can only be concluded after a thorough workup performed by a neurologist and a cardiologist, where the neurologist mainly diagnoses cryptogenic stroke and the cardiologist estimates the risks and benefits of the closing procedure. Patients with TIA, with a high cardiovascular risk profile, or with a non-cryptogenic stroke attributed to a non-paradoxical event are no good candidates for PFO closure. Finally, the benefits of PFO closure have to outweigh the potential risks of the closing procedure. PFO closure is preferably performed in experienced centres.

CONFLICT OF INTEREST: none declared.

REFERENCES

1. Windecker S, Meier B. Is closure recommended for patent foramen ovale and cryptogenic stroke? Patent foramen ovale and cryptogenic stroke: to close or not to close? Closure: what else! *Circulation* 2008; **118**: 1989-98.
2. Moore K. *The Developing Human: Clinically Oriented Embryology*. Ed. 6, Philadelphia, PA, Saunders, 1998.
3. Olivares-Reyes A, Chan S, Lazar EJ, Bandlamudi K, Narla V, Ong K. Atrial septal aneurysm: a new classification in two hundred five adults. *J Am Soc Echocardiogr* 1997; **10**: 644-56.
4. Marazanof M, Roudaut R, Cohen A, Tribouilloy C, Malergues MC, Halphen C, Bussiere JL, Schultz R, Marcaggi X, Lardoux H, Bruntz JF, Coisnes D, Brandt CM, Marchal C, Letenneur L, Bonnet J. Atrial septal aneurysm. Morphological characteristics in a large population: pathological associations. A French multicenter study on 259 patients investigated by transoesophageal echocardiography. *Int J Cardiol* 1995; **52**: 59-65.
5. Vick GW. Defects of the atrial septum including atrioventricular septal defects. In: Garson A, Jr, Bricker JT, Fisher DJ, Neish SR. *The Science and Practice of Pediatric Cardiology*, 2nd edition. Baltimore, MD: Williams & Wilkins, 1998: 1141-79.
6. Lynch JJ, Schuchard GH, Gross CM, Wann LS. Prevalence of right-to-left atrial shunting in a healthy population: detection by Valsalva maneuver contrast echocardiography. *Am J Cardiol* 1984; **53**: 1478-80.
7. Sloan MA, Alexandrov AV, Tegeler CH, Spencer MP, Caplan LR, Feldmann E, Wechsler LR, Newell DW, Gomez CR, Babikian VL, Lefkowitz D, Goldman RS, Armon C, Hsu CY, Goodin DS. Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2004; **62**: 1468-81.

8. Di Tullio M, Sacco RL, Venketasubramanian N, Sherman D, Mohr JP, Homma S. Comparison of diagnostic techniques for the detection of a patent foramen ovale in stroke patients. *Stroke* 1993; **24**: 1020-4.
9. Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, Drobinski G, Thomas D, Grosgogeat Y. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988; **318**: 1148-52.
10. Lamy C, Giannesini C, Zuber M, Arquizan C, Meder JF, Trystram D, Coste J, Mas JL. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. Atrial Septal Aneurysm. *Stroke* 2002; **33**: 706-11.
11. Elijovich L, Josephson SA, Fung GL, Smith WS. Intermittent atrial fibrillation may account for a large proportion of otherwise cryptogenic stroke: a study of 30-day cardiac event monitors. *J Stroke Cerebrovasc Dis* 2009; **18**: 185-9.
12. Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? *Stroke* 2009; **40**: 2349-55.
13. Martin F, Sanchez PL, Doherty E, Colon-Hernandez PJ, Delgado G, Inglessis I, Scott N, Hung J, King ME, Buonanno F, Demirjian Z, de Moor M, Palacios IF. Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Circulation* 2002; **106**: 1121-6.
14. Meier B. Closure of patent foramen ovale: technique, pitfalls, complications, and follow up. *Heart* 2005; **91**: 444-8.
15. Windecker S, Wahl A, Chatterjee T, Garachemani A, Eberli FR, Seiler C, Meier B. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. *Circulation* 2000; **101**: 893-8.
16. Krumsdorf U, Ostermayer S, Billinger K, Trepels T, Zadan E, Horvath K, Sievert H. Incidence and clinical course of thrombus formation on atrial septal defect and patient foramen ovale closure devices in 1,000 consecutive patients. *J Am Coll Cardiol* 2004; **43**: 302-9.
17. De Castro S, Cartoni D, Fiorelli M, Rasura M, Anzini A, Zanette EM, Beccia M, Colonnese C, Fedele F, Fieschi C, Pandian NG. Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke* 2000; **31**: 2407-13.
18. Lee JY, Song JK, Song JM, Kang DH, Yun SC, Kang DW, Kwon SU, Kim JS. Association between anatomic features of atrial septal abnormalities obtained by omni-plane transesophageal echocardiography and stroke recurrence in cryptogenic stroke patients with patent foramen ovale. *Am J Cardiol* 2010; **106**: 129-34.
19. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, Felberg R, Herrmann H, Kar S, Landzberg M, Raizner A, Wechsler L. Study design of the CLOSURE I Trial: a prospective, multicenter, randomized, controlled trial to evaluate the safety and efficacy of the STARFlex septal closure system versus best medical therapy in patients with stroke or transient ischemic attack due to presumed paradoxical embolism through a patent foramen ovale. *Stroke* 2010; **41**: 2872-83.
20. Khattab AA, Windecker S, Juni P, Hildick-Smith D, Dudek D, Andersen HR, Ibrahim R, Schuler G, Walton AS, Wahl A, Mattle HP, Meier B. Randomized clinical trial comparing percutaneous closure of patent foramen ovale (PFO) using the Amplatzer PFO Occluder with medical treatment in patients with cryptogenic embolism (PC-Trial): rationale and design. *Trials* 2011; **12**: 56.
21. O'Gara PT, Messe SR, Tuzcu EM, Catha G, Ring JC. Percutaneous device closure of patent foramen ovale for secondary stroke prevention: a call for completion of randomized clinical trials. A science advisory from the American Heart Association/ American Stroke Association and the American College of Cardiology Foundation. *J Am Coll Cardiol* 2009; **53**: 2014-8.
22. O'Gara PT, Messe SR, Tuzcu EM, Catha G, Ring JC. Percutaneous device closure of patent foramen ovale for secondary stroke prevention: a call for completion of randomized clinical trials: a science advisory from the American Heart Association/ American Stroke Association and the American College of Cardiology Foundation. *Circulation* 2009; **119**: 2743-7.
23. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Schwamm LH, Tomsick T. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Circulation* 2006; **113**: e409-449.
24. Torti SR, Billinger M, Schwerzmann M, Vogel R, Zbinden R, Windecker S, Seiler C. Risk of decompression illness among 230 divers in relation to the presence and size of patent foramen ovale. *Eur Heart J* 2004; **25**: 1014-20.
25. Cheng TO. Transcatheter closure of patent foramen ovale: a definitive treatment for platypnea-orthodeoxia. *Catheter Cardiovasc Interv* 2000; **51**: 120.
26. Budts W. Relationship between migraine and right-to-left shunt in children: editorial. *Eur J Pediatr 2011*; **170**: 275-7.
27. Post MC, Budts W. The relationship between migraine and right-to-left shunt: Fact or fiction? *Chest* 2006; **130**: 896-901.
28. Dowson A, Mullen MJ, Peatfield R, Muir K, Khan AA, Wells C, Lipscombe SL, Rees T, De Giovanni JV, Morrison WL, Hildick-Smith D, Elrington G, Hillis WS, Malik IS, Rickards A: Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. *Circulation* 2008; **117**: 1397-1404.
29. Tepper SJ, Cleves C, Taylor FR. Patent foramen ovale and migraine: association, causation, and implications of clinical trials. *Curr Pain Headache Rep* 2009; **13**: 221-6.
30. Bonvini RF, Sztajzel R, Dorsaz PA, Righini M, Bonvin C, Alibegovic J, Sigwart U, Camenzind E, Verin V, Sztajzel J. Incidence of atrial fibrillation after percutaneous closure of patent foramen ovale and small atrial septal defects in patients presenting with cryptogenic stroke. *Int J Stroke* 2010; **5**: 4-9.
31. Wahl A, Krumsdorf U, Meier B, Sievert H, Ostermayer S, Billinger K, Schwerzmann M, Becker U, Seiler C, Arnold M, Mattle HP, Windecker S. Transcatheter treatment of atrial septal aneurysm associated with patent foramen ovale for prevention of recurrent paradoxical embolism in high-risk patients. *J Am Coll Cardiol* 2005; **45**: 377-80.
32. Shafi NA, McKay RG, Kiernan FJ, Silverman IE, Ahlquist M, Silverman DI. Determinants and clinical significance of persistent residual shunting in patients with percutaneous patent foramen ovale closure devices. *Int J Cardiol* 2009; **137**: 314-6.