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Patent Foramen Ovale — Beauty Spot or Health Threat?

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In 1877, Cohnheim first suggested a potential causal relationship of a patent foramen ovale (PFO) with significant disease when analyzing the case of a young woman with a stroke.[1] Today, this correlation is well founded and uncontested. This issue of *Cardiology Rounds* reviews the etiology of a patent foramen ovale, the diagnostic methods for PFO, the relationship between PFO and strokes and other clinical problems, as well as methods of closure. The latter discussion emphasizes percutaneous transcatheter closure, which, in the author's opinion, is the most clinically viable treatment available at present.

History of the association of cryptogenic embolism and PFO

During embryogenesis (Figure 1), the left-sided septum primum and the right-sided septum secundum form by growing from the walls towards the center of the interatrial area. Each leaves a gap in a position that facilitates the crossing – through the interatrial septum – of blood arriving from the placenta through the inferior vena cava, thereby bypassing the lungs. Since the caudad part of the septum primum is overlying the cephalad part of the septum secundum (Figure 1a), the foramen ovale only opens when pressure on the right side is higher than that on the left side.

After birth, the lungs unfold and the pressure of the left atrium supercedes that of the right atrium; the septum primum is pushed against the septum secundum, keeping the foramen ovale closed. This usually results in fusion, engendering a solid interatrial septum (Figure 1b). In about 25% of the population, the two septa remain separable and the foramen may open during moments when the right atrial pressure overrides the left atrial pressure, or from the mere velocity of blood pounding against the septum (Figure 1c). This provides an opportunity for clots originating in the venous system to cross into the arterial system, bypassing the lung filter. The crossing of a large clot is a rare event, but it allows for unmistakable proof of the mechanism of paradoxical embolism and for diagnosis by echocardiography (Figure 2).[2] A much more common occurrence is paradoxical embolism of small clots (measuring a few mm). Such clots can neither be detected in the venous system, nor during their migration or passage through the PFO. It is only their effect after occluding an end-artery (above all in the brain or the heart) that they become clinically apparent.

Diagnosis of patent foramen ovale

The diagnosis of a PFO during the work-up for a cryptogenic stroke, considered to be paradoxical, is generally done with transesophageal echocardiography (Figure 3). The sensitivity of transthoracic echocardiography for this diagnosis is insufficient as it can rarely be ascertained that the bubbles pass through the PFO. Bubbles appearing in the left atrium several heart beats after they appeared in the right atrium, may represent an intrapulmonary shunt rather than a PFO.

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Figure 1: Embryogenesis of the interatrial septum.

Figure 1a: In the prenatal heart, the septum primum on the left side and the septum secundum (gray area) on the right side grow from the periphery to the center without closing the gap completely. Septum primum and septum secundum have fused longitudinally. The initial gaps (septum primum more cephalad and septum secundum more caudad) form a channel in line with the blood from the placenta arriving from the inferior vena cava. This blood keeps the foramen ovale open. The foramen ovale forms a valve that is ready to close as soon as the pressure in the LA supercedes that of the RA.

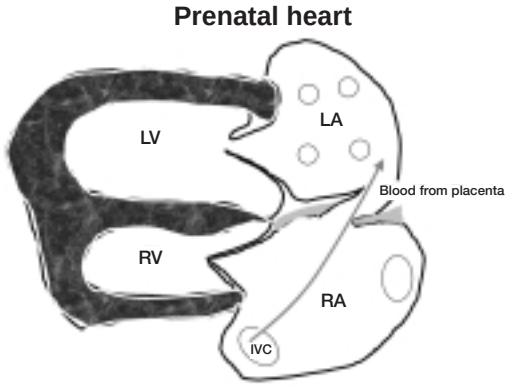


Figure 1b: After birth, the caudad part of the septum is pushed against the cephalad part and the overlying segments fuse within weeks.

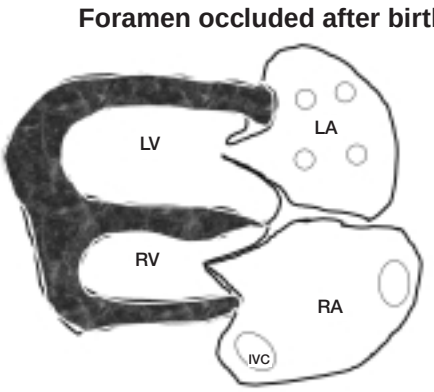
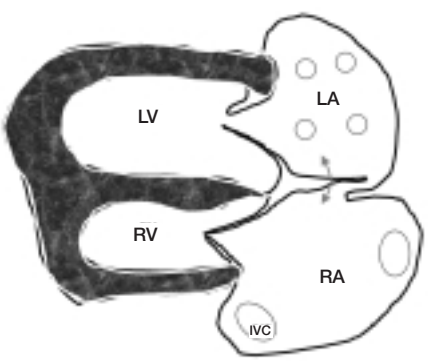
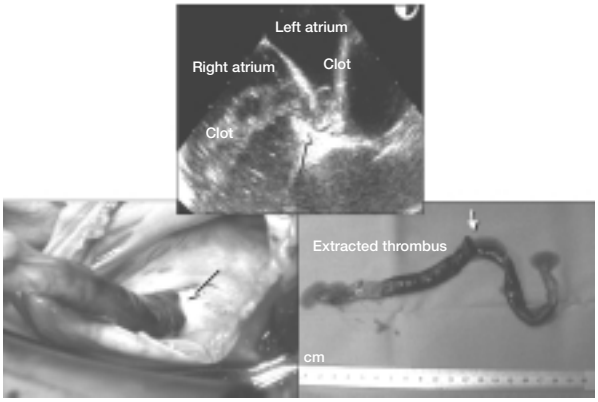


Figure 1c: In about 25% of the population this fusion fails to occur and the foramen ovale remains patent (PFO). This means it will open or close (bi-headed arrow) according to blood pressure and blood flow on both sides. The most common cause of opening is a gush of blood arriving at the right atrium after a prolonged Valsalva maneuver (defecation, childbirth, coughing, etc.), flooding the RA while the LA is still empty.



IVC = inferior vena cava; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Figure 2: Huge thrombus (about 30 cm long) having transgressed halfway through the PFO in a 45-year-old man. The problem was detected by the clinical picture of pulmonary emboli. These were probably caused by fragments severed off the tail of the thrombus swinging between the right ventricle and the inferior vena cava. The clot was detected by transesophageal echocardiography (top panel). It was removed surgically (bottom panel). It must have originated from a large vein in the thigh of the patient. The arrows indicate the segment of the thrombus stuck in the PFO.



The experienced eye can determine that bubbles passing through a pulmonary shunt are usually smaller than the average bubbles in the right atrium. Larger ones rarely pass through a pulmonary shunt, while they regularly pass through a PFO.

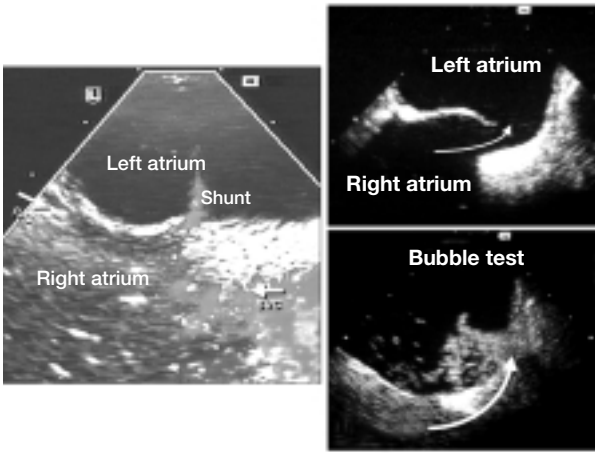
Alternative methods to diagnose a PFO are currently secondary, but may play a more important role in the future. The assessment of the number of HITS (high intensity transient signals) by transcranial Doppler recordings needs improvement in terms of its specificity.[3] Computer tomography and magnetic resonance are likely to match the sensitivity or specificity of transesophageal echocardiography, but at present, are less readily available and more expensive. The diagnostic yield of skin oximetry (rapid and transient drop in saturation after release of a Valsalva maneuver) is under investigation.

Patent foramen ovale and stroke

It has been estimated that about 750,000 strokes occur yearly in the United States, with a mortality of 27%. This makes stroke the third leading cause of death behind heart disease and cancer. About 80% of strokes are of ischemic origin, the remainder being hemorrhagic.

Cryptogenic stroke (when no source of embolism is detectable) accounts for about 40% of strokes in young adults.[4-6] Contrast echocardiography reveals that there is a clear prevalence of PFOs in adults who are <55 years with cryptogenic stroke,[7-12] but not in the elderly.[7,10,11,13] In a meta-analysis of case-control studies, the association between ischemic stroke and PFO was confirmed.[14] The odds-ratios of different patient groups are reflected in Table 1. In the same overview, the role of an atrial septal aneurysm was assessed. An atrial septal aneurysm is 10 times less common than a PFO and is formed by a flimsy and redundant septum primum that moves with cardiac

Figure 3: Transesophageal echocardiography demonstrating a shunt (spontaneously only left-to-right, after Valsalva maneuver also right-to-left) by Doppler (left panel). The gaping of the PFO (right panel, top) with the thin septum primum on top and to the left and thicker septum secundum on the bottom and to the right, is clearly visible in this picture but may be misleading. Only the clear evidence of passage of microbubbles (ECG contrast medium with aerated colloid or saline solution) proves the PFO (right panel, bottom). This requires a prolonged Valsalva maneuver with the injection of bubbles (bubble test) just before its release. The flow entering the right atrium from the superior vena cava (SVC) runs in a direction opposite to the passage through the PFO, while the flow from the inferior vena cava (IVC) flows along the interatrial septum to invariably find the PFO (left panel). This makes the diagnosis of a PFO by bubble injection through the arm more difficult. In case of doubt, an injection into a femoral vein is recommended.



motion towards the left or right atrium (Figure 4). The echocardiographic definition is excursion in either direction of more than 10 mm. Initially, an atrial septal aneurysm was considered a risk factor *per se* for left-sided embolic events. Recently, however, the Stroke Prevention Assessment of Risk in a Community (SPARC) study identified an atrial septal aneurysm as a risk enhancer in the presence of a PFO, rather than an independent source of embolism.[15]

Other risk factors contributing to the danger of a PFO are less well explored. The eustachian valve, a remnant of a membrane leading the blood from the inferior vena cava directly to the foramen ovale during intrauterine life (Figure 5), has been anecdotally indicated as an associate culprit. It may play a particularly important role in the disease entity called platypnea orthodeoxia. In this syndrome, mostly elderly people experience severe systemic hypoxia due to a massive right-to-left shunt while assuming an erect position. Their right atrial pressure may remain well below the left atrial pressure. The shunt is caused by the mere flow of blood from the inferior vena cava directed (eg, by a eustachian valve) straight to the mobile septum primum in the presence of a PFO.[16]

Further situations fostering right-to-left shunt are right atrial hypertension in the setting of chronic pulmonary disease or recurrent pulmonary embolism. Finally, coagulation disorders, such as pro-thrombotic genetic polymorphisms (factor V Leiden mutation, anticardiolipin

Table 1: The role of a PFO in stroke patients[14]

	Odds ratio (95% CI)		
	PFO	ASA	PFO+ASA
All ages			
Stroke versus non stroke controls	2 (1-2)	2 (2-3)	5 (3-10)
Cryptogenic stroke versus known stroke cause	3 (3-4)	3 (2-3)	21 (4-104)
Cryptogenic stroke versus non-stroke controls	3 (2-3)	4 (3-6)	24 (3-185)
Age < 55 years			
Stroke versus non stroke controls	3 (2-4)	6 (3-15)	16 (3-86)
Cryptogenic stroke versus known stroke cause	6 (4-10)	7 (2-31)	17 (2-133)
Cryptogenic stroke versus non-stroke controls	5 (3-8)	19 (3-150)	24 (3-185)
Age ≥ 55 years			
Stroke versus non stroke controls	1 (1-2)	3 (12-6)	5 (1-21)
Cryptogenic stroke versus known stroke cause	2.0 (1-3)		
Cryptogenic stroke versus non-stroke controls	1 (1-3)		

antibodies, protein C or S deficiencies, pro-thrombin G20210A mutation) or thrombocytosis are of importance.

The etiologic role of the PFO itself for stroke can be deduced from the fact that its prevalence in a normal population at autopsy is about 26%,[17-27] while the average prevalence in patients <55 years with cryptogenic stroke is about 50%.[7-12] In contrast, in patients >55 years with cryptogenic stroke, there is no preponderance of PFOs (Table 1).[7,10,11,13]

In addition, the size of a PFO and the number of bubbles passing through are well-identified risk factors for cryptogenic stroke. In one study, PFO carriers with a cryptogenic stroke had a maximum dehiscence of 2.1 ± 1.7 mm compared with 0.6 ± 0.8 mm of control PFO carriers, and the bubbles countable on a still frame in the left atrium during transesophageal echocardiography amounted to 14 ± 11 compared with 2 ± 1, respectively.[28]

Other problems associated with PFO

Additional clinical entities or situations have been identified that represent potential indications for PFO

Figure 4: Atrial septal aneurysm showing the mobile septum primum (SP) in its maximal left position far into the left atrium (LA) (**Left panel:** the two + signs indicate the associated PFO; **center panel:** in a relaxed position; and in the **right panel:** a bizarrely folded position just before prolapsing into the right atrium (RA)). The septum secundum (SS) is solid and immobile. A few remaining bubbles from a contrast study are visible in the RA.

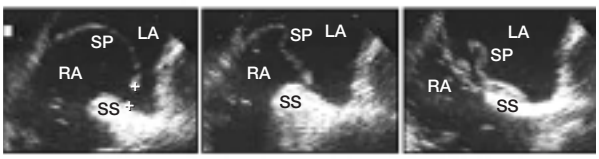
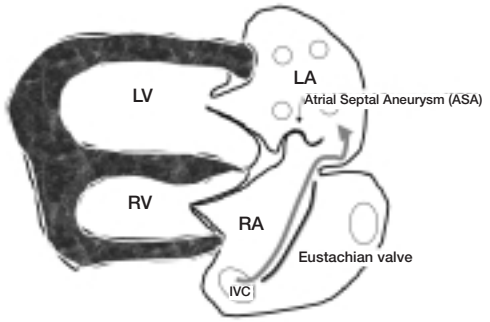


Figure 5: Graphic rendering of the 2 most common anatomical risk factors, in addition to the diameter of the opening itself, instrumental for increased risk of paradoxical embolism. The atrial septal aneurysm (ASA) is always confined to the caudad part of the septum, predominantly consisting of the septum primum. The eustachian valve is the remnant of a membrane directing the blood from the inferior vena cava to the foramen during pregnancy. This membrane should disappear after birth or at least no longer be directed towards the fossa ovalis after the atrium has grown.



closure. In divers, it has been shown that decompression problems led to more brain defects in individuals with a PFO than in those without.[29,30] It was also found that the prevalence of migraines was high in patients with a PFO. Surprisingly, with PFO closure for suspicion of paradoxical embolism, almost half of the patients reported cessation of migraines (Figure 6).[31]

A PFO may be especially dangerous during surgical interventions that are prone for embolization of fat (orthopedic surgery) or air (neurosurgery, cardiovascular surgery) into the venous system.[32]

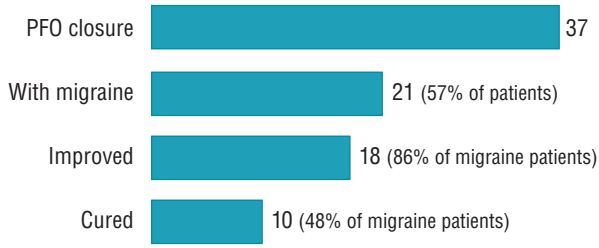
Risk of recurrence after cryptogenic embolism

Conservative treatment after presumed paradoxical embolism in the brain, consists of either coumadin or platelet inhibition by acetylsalicylic acid. Studies with the new platelet inhibitor, clopidogrel, are underway. The Warfarin Aspirin Recurrence Strokes Study (WARSS) yielded a surprisingly high incidence of recurrent strokes or death over two years (15% with warfarin and 17% with acetylsalicylic acid), when only patients with cryptogenic strokes were considered.[33] Earlier studies have shown lower incidences of recurrent cerebral events (Table 2).[34-38] Looking at the combined endpoint of cerebrovascular accidents or transient ischemic attacks (TIAs), 3% to 5% emerges as a reasonable estimate of risk of recurrence during the first year under medical treatment. It is likely that patients with the risk factors enumerated above are at an even higher risk.

Surgical closure of patent foramen ovale

Table 3 depicts the results of surgical closure reported in the literature.[39-42] The recurrence rates vary considerably. A 4% combined incidence of cerebrovascular attacks and TIAs, as reported from the Mayo Clinic in 1999, appears most reliable, although this study encompassed only 91 patients, with a follow-up of 4 years.[42] Surgical closure is

Figure 6: Prevalence of migraine and follow-up in a small group of patients with successful PFO closure for suspicion of paradoxical embolism. More than half of the patients had migraine. Among them, almost 90% reported improvement and about half were cured.[31]



well established, safe (for mostly young and otherwise healthy patients) and successful; however, it is not free from residual shunts or recurrent events. In addition, morbidities such as wound infection, scar problems, negative effects of the heart-lung machine, and the need for several days of hospitalization may occur. Surgical closure has recently been largely replaced by percutaneous closure.

Percutaneous transcatheter closure of a PFO

History

The first percutaneous closure of an atrial septal defect (ASD) was performed in 1974 and was reported by King in 1976.[43] This device was not pursued further, but in the 80s, Rashkind developed the Clamshell occluder[44] that was subsequently modified by Lock into the CardioSEAL and then the StarFlex device (Figure 7). The device was conceived for ASD closure, but it was logical to also use it for PFO closure. Later,

- Sideris introduced the Buttoned Device[45] (Figure 7),
- Babic, the ASDOS Device,[46]
- Pavcnik, the Monodisk,[47]
- Das, the Angel-Wings Device, subsequently transformed into the Guardian Angel Device[48] (Figure 7), and
- Amplatz, the Amplatzer ASD Closure Device.[49]

The 90s saw the appearance of devices dedicated exclusively to PFO closure. The first was the Amplatzer PFO Occluder (Figure 7) with the world's first implantation by the author on September 10, 1997.[50] Then, there was the PFO Star (Figure 7).[51] The latest device – the

Table 2: Recurrence with medical therapy after cryptogenic stroke

Reference	Patients	Follow-up (months)	First year CVA recurrence	First year CVA or TIA recurrence
Comess[34]	33	12		16%/year
Hanna[35]	13	41	0%	
Mas[36]	132	22	1.2%	3.4%
Bogousslavsky[37]	140	36	1.9%	3.8%
De Castro[38]	86	36	4.2%	5.5%

CVA = cerebrovascular accident; TIA = transient ischemic attack

Table 3: Surgical results of closure of PFO

Reference	Patients	Follow-Up (Months)	First Year CVA Recurrence	First Year CVA or TIA Recurrence
Zhu[39]	6	48	8.2%	
Devuyst[40]	30	24	0%	0%
Homma[41]	28	19	3.6%	19.5%
Dearani[42]	91	48	0%	4.1%

CVA = cerebrovascular accident; TIA = transient ischemic attack

Helex Device (Figure 7)[52] – is again also targeted for ASDs.

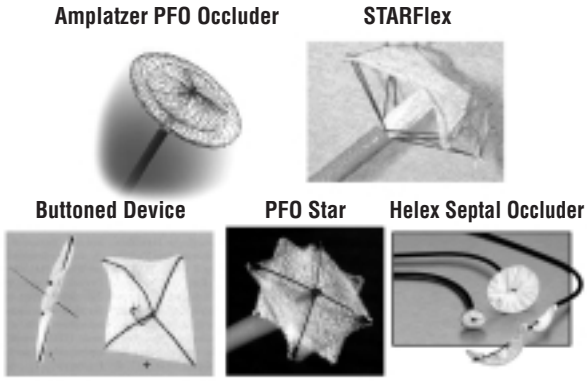
Technique

The technique for implantation varies among centers. Table 4 lists a proposal for a simple technique. Echocardiographic guidance is not necessary, nor is gauging the size of the PFO with a balloon catheter. Provided there is a good visualization of the PFO by transesophageal echocardiography before the intervention, the implantation is easily guided by fluoroscopy alone. The left-sided part of the device is opened and pulled back against the septum. This is felt, as opposed to visualized, since the septum cannot be seen on fluoroscopy. It is almost impossible to inadvertently pull the device through the septum. This can be explained by the analogy of pushing a closed umbrella through a partially opened door, then opening the umbrella on the other side and pulling it back. It will not slip back through the door as it will close the door while being pulled back. Before release and again after release, the position can easily be assessed by a manual contrast medium injection through the introducer sheath (Figure 8). The contrast can be followed through the lungs to the left atrium. This allows assessment of the alignment of the left-sided disk with the left atrial side of the septum (Figure 8). Some centers use guidance by transesophageal echocardiography, but this is quite cumbersome for the patient and

Table 4: Technique of percutaneous PFO closure

- ≤ 1 night at hospital
- Local anesthesia
- Access: right femoral vein
- No balloon gauging
- No echocardiographic guidance
- Multipurpose catheter to cannulate PFO
- 0.035 inch (exchange) wire
- 6 - 14 French transseptal sheath
- Right atrial dye injections (by hand, LAO cranial)
- Antibiotics (1 - 3 doses)
- Acetylsalicylic acid 100 mg for 6 months and clopidogrel 75 mg for 1 month
- Final transesophageal echocardiography control at 6 months

Figure 7: Percutaneous occluders currently available for clinical use. Top left: the Amplatzer PFO occluder is worldwide by far the most widely used device (right-sided disk larger than left-sided). It yields the best clinical results. **Top right:** the StarFlex occluder is currently the only one available in the United States. **Bottom panel:** the Buttoned Device, the PFO Star and the Helex Septal Occluder are depicted from left to right in the order of their appearance on the market.



may even require full anesthesia with intubation because of the supine position.

The method and duration of anticoagulation or platelet inhibition is controversial. Our experience without coumarin in more than 300 patients using atrial devices, showed only two demonstrable thrombi without clinical events, one on the right and one on the left side. It can be assumed that treatment with platelet inhibitors is safe and that the devices are sufficiently endothelialized within a few weeks. Figure 9 depicts a device implanted for 4 months and one for 4 hours in the same patient; the patient was treated with clopidogrel for 1 month and acetylsalicylic acid for 4 months.

Indications

The indications that are currently maintained by most centers, but have yet to be proven clinically, are listed in Table 5. With some non-paradoxical reasons for embolism

Figure 8: Manual injection of 5-10 ml of contrast medium in a left anterior oblique projection through the 8 French introducer sheath allows to document the perfect position of a 25 mm Amplatzer PFO occluder before and after release. The **left panel** shows the opacification of the right atrium (RA). The **right panel** shows the diluted dye opacifying the left atrium (LA) after having passed through the lung. The border of the LA is enhanced with a dotted line.

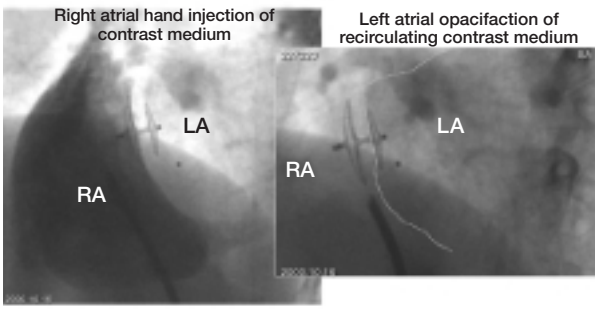


Table 5: Indications of percutaneous PFO closure

- History of unequivocal and unexplained systemic embolism(s)
- Non-paradoxical source of embolism excluded by
  - ultrasound of
    - cerebral arteries
    - heart (transesophageal echocardiogram)
    - aorta
  - 24 hour electrocardiogram
  - screening for hypercoagulability
- PFO documented by echocardiography (spontaneous or provoked (period after Valsalva maneuver) shunt or bubble transit)
  - transthoracically, if clearly visible
  - transesophageally, if not clear transthoracically (period after Valsalva maneuver)

such as atrial fibrillation or hypercoagulability, it can be questioned whether the PFO should be closed anyway, at least to eliminate the embolic sources on the right side of the circulation.

Clinical results

In 250 consecutive patients subjected to percutaneous closure of a PFO, two PFOs could not be found. One was a residual leak after surgical correction and one was a small hole in an atrial septal aneurysm. Hence, both failures to canulate the PFO were explained by the fact that there was no real PFO. One patient needed vascular surgery because of a puncture problem before the device could be introduced and the other needed needle pericardiocentesis for hemorrhagic pericardial effusion. The patients ranged in age from 18 to 75 years, with a mean of 51 years. The male/female ratio was balanced. The mean duration of the procedure was <30 minutes and the fluoroscopy time was

Figure 9: Amplatzer ASD occluders (identical surface properties with PFO occluders) explanted from the heart of a 21-year-old woman 4 months after the implantation of the left device and 4 hours after the implantation of the right device during surgical closure of a large fenestrated atrial septal defect in which the second device could not be successfully placed. The left device is fully endothelialized by a glistening layer of endocardium while the freshly implanted device only shows some fibrin between the wire meshes. There is no sign of thrombosis on either device (view from the right side with the small right-sided disk of the ASD occluder in front).

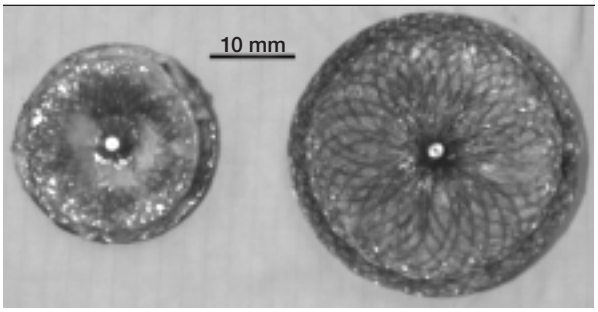
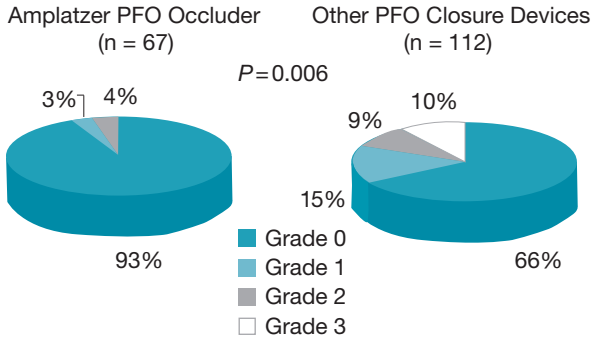


Figure 10: Residual shunt at follow-up transesophageal echocardiography after PFO occlusion with the Amplatzer PFO occluder (left panel) compared with other occluders (right panel). Grade zero: no residual shunt. Grade three: more than 25 bubbles visible on a still frame in the left atrium. The results with the Amplatzer PFO Occluder are significantly superior.



5 minutes. Follow-up after at least 6 months revealed that the performance of the Amplatzer PFO occluder was superior (7% residual shunts compared with 34% for all other devices combined, Figure 10).

As for clinical events, the average rate of recurrent TIAs or peripheral embolism was 1.6% per year in the first 170 patients with sufficient follow-up. Cerebrovascular accidents did not occur and there was no mortality. This compares favorably with the natural course reported recently by De Castro et al (Figure 11).[38] There was no difference in our series at the Swiss Cardiovascular Center Bern regarding PFO closures, whether an atrial septal aneurysm was present (1.5% events per year) or not (1.6%). However, patients with complete closure fared better (1.0% events per year) than those with residual shunts (3.4%, $P = 0.03$).

Comparing our patients with a control group followed medically at our center, there was again a lower incidence of recurrent events after the first 2 years. The difference reached statistical significance for major strokes (0% with closure and 2.3% per year with medical treatment). There was also a significant advantage for patients with 2 or more prior events and for those with complete closure.

Summary and conclusions

Clearly, a PFO can have clinical importance. The fact that children rarely show paradoxical embolism can be explained by their extremely low potential for thrombosis in the venous system. The older a person gets, however, the more likely a paradoxical embolism if there is a PFO. However, left-sided embolic sources increase with age in an even more marked manner so that a PFO is of peak clinical importance in middle-aged people.

Until the results of ongoing randomized trials are available, matched and unmatched comparisons with conventional treatment offer the best available data. They appear to favor PFO closure. They also show that the closure yields better results if it is complete. This may give

Figure 11: Comparison of combined endpoints during follow-up in our series (triangles) and a report on the natural course of patients with cryptogenic embolism. Starting with the third year, there appears to be an advantage for PFO closure. However, this is not a randomized or matched comparison.[38]

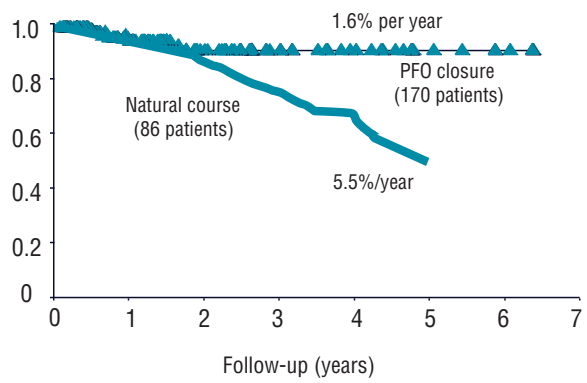
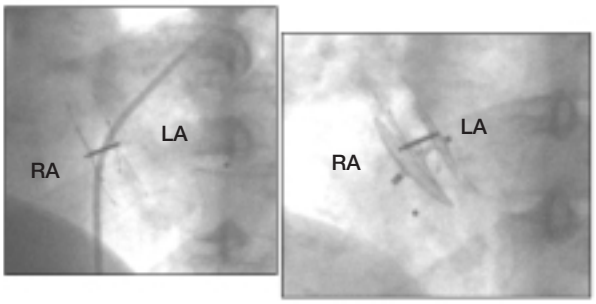


Figure 12: Implantation of an Amplatzer PFO occluder (25 mm) 6 months after incomplete closure of a PFO with a PFOStar (30 mm) in a 34-year-old woman who had no recurrent event, but was worried about the incomplete closure.
The left panel shows a left atrial dye injection through a diagnostic catheter passed easily through the residual shunt at the site of the correctly positioned PFOStar.
The right panel shows the Amplatzer occluder straddling the PFOStar device. The left atrium is again slightly opacified by dye.



LA = left atrium; RA = right atrium.

a reason for a second device closure in case of a residual leak (Figure 12).

For the time being, it seems acceptable to attempt percutaneous closure in patients who desire it after full explanation of the advantages and disadvantages. It also seems acceptable to recommend closure to patients with a high risk of further events, (ie, those with several previous embolic events, with an atrial septal aneurysm, or a tendency for venous thrombosis). There are also professional divers who may want their PFO closed, and the odd case of platypnea orthodeoxia. Migraine is not yet an indication, but this topic needs to be pursued further.

Surgical closure can be kept in reserve. None of the patients in our series needed it subsequently, but all could have been operated upon without problems if the need had arisen after attempted percutaneous closure.

References:

1. Cohnheim J. In: *Thrombose und Embolie: Vorlesung über allgemeine Pathologie*. Berlin, Germany: Hirschwald, Berlin (Publishers); 1877:134.
2. Srivastava TN, Payment MF. Images in clinical medicine. Paradoxical embolism--thrombus in transit through a patent foramen ovale. *N Engl J Med* 1997;337:681.
3. Droste DW, Ringelstein EB. Detection of high intensity transient signals (HITS): how and why? *Eur J Ultrasound* 1998;7:23-29.
4. Hart RG, Miller VT. Cerebral infarction in young adults: a practical approach. *Stroke* 1983;14:110-114.
5. Sacco RL, Ellenberg JH, Mohr JP, et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. *Ann Neurol* 1989;25:382-390.
6. Steiner MM, Di Tullio MR, Rundek T, et al. Patent foramen ovale size and embolic brain imaging findings among patients with ischemic stroke. *Stroke* 1998;29:944-948.
7. Hausmann D, Mugge A, Becht I, Daniel WG. Diagnosis of patent foramen ovale by transesophageal echocardiography and association with cerebral and peripheral embolic events. *Am J Cardiol* 1992;70: 668-672.
8. Webster MW, Chancellor AM, Smith HJ, et al. Patent foramen ovale in young stroke patients. *Lancet* 1988;2:11-12.
9. Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988;318:1148-1152.
10. De Belder MA, Tourikis L, Leech G, Camm AJ. Risk of patent foramen ovale for thromboembolic events in all age groups. *Am J Cardiol* 1992;69:1316-1320.
11. Di Tullio M, Sacco RL, Gopal A, Mohr JP, Homma S. Patent foramen ovale as a risk factor for cryptogenic stroke. *Ann Intern Med* 1992; 117:461-465.
12. Cabanes L, Mas JL, Cohen A, et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. *Stroke* 1993;24:1865-1873.
13. Jones EF, Calafiore P, Donnan GA, Tonkin AM. Evidence that patent foramen ovale is not a risk factor for cerebral ischemia in the elderly. *Am J Cardiol* 1994;74:596-599.
14. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000; 55:1172-1179.
15. Meissner I, Whisnant JP, Khandheria BK, et al. Prevalence of potential risk factors for stroke assessed by transesophageal echocardiography and carotid ultrasonography: the SPARC study. Stroke Prevention: Assessment of Risk in a Community. *Mayo Clin Proc* 1999;74:862-869.
16. Cheng TO. Platypnea-orthodeoxia syndrome: etiology, differential diagnosis, and management. *Catheter Cardiovasc Interv* 1999;47:64-66.
17. Parsons FG, Keith A. Seventh report of the Committee of Collective Investigation of theAnatomical Society of Great Britain and Ireland, for the years 1896-1897. *J Anat Physiol* 1897;32:164-186.
18. Fawcett E, Blachford JV. The frequency of an opening between the right and left auricles at the seat of the foetal foramen ovale. *J Anat Physiol* 1900;35:67-70.
19. Scammon RE, Norris EH. On the time of the post-natal obliteration of the fetal blood-passages (foramen ovale, ductus arteriosus, ductus venosus). *Anat Rec* 1918;15:165-180.
20. Thompson T, Evans W. Paradoxical embolism. *Quart J Med* 1930;23: 135-150.
21. Patten BM. The closure of the foramen ovale. *Am J Anat* 1931;48:19-44.
22. Seib GA. Incidence of the patent foramen ovale cordis in adult American whites and American negroes. *Am J Anat* 1934;55:511-525.
23. Wright RR, Anson BJ, Cleveland HC. The vestigial valves and the interatrial foramen of the adult human heart. *Anat Rec* 1948;100:331-335.
24. Schroeckenstein RF, Wasenda GJ, Edwards JE. Valvular competent patent foramen ovale in adults. *Minn Med* 1972;55:11-13.
25. Sweeney LJ, Rosenquist GC. The normal anatomy of the atrial septum in the human heart. *Am Heart J* 1979;98:194-199.
26. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984;59:17-20.
27. Penther P. Patent foramen ovale: an anatomical study. A propos of 500 consecutive autopsies. *Arch Mal Coeur Vaiss* 1994;87:15-21.
28. Homma S, Di Tullio MR, Sacco RL, Mihalatos D, Li Mandri G, Mohr JP. Characteristics of patent foramen ovale associated with cryptogenic stroke. A biplane transesophageal echocardiographic study. *Stroke* 1994;25:582-586.

29. Knauth M, Ries S, Pohimann S, et al. Cohort study of multiple brain lesions in sport divers: role of a patent foramen ovale. *BMJ* 1997; 314:701-705.
30. Schwerzmann M, Seiler C, Lipp E, et al. Relation between directly detected patent foramen ovale and ischemic brain lesions in sport divers. *Ann Intern Med* 2001;134:21-24.
31. Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. *Lancet* 2000;356:1648-1651.
32. Sukernik MR, Mets B, Bennett-Guerrero E. Patent foramen ovale and its significance in the perioperative period. *Anesth Analg* 2001;93: 1137-1146.
33. Mohr JP, Thompson JLP, Lazar RM, et al, For the Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *New Engl J Med* 2001; 345:1444-1451.
34. Comess KA, De Rook FA, Beach KW, Lytle NJ, Golby AJ, Albers GW. Transesophageal echocardiography and carotid ultrasound in patients with cerebral ischemia: prevalence of findings and recurrent stroke risk. *J Am Coll Cardiol* 1994;23:1598-1603.
35. Hanna JP, Sun JP, Furlan AJ, Stewart WJ, Sila CA, Tan M. Patent foramen ovale and brain infarct. Echocardiographic predictors, recurrence, and prevention. *Stroke* 1994;25:782-786.
36. Mas JL, Zuber M. Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. *Am Heart J* 1995; 130:1083-1088.
37. Bogousslavsky J, Garazi S, Jeanrenaud X, Aebischer N, Van Melle G. Stroke recurrence in patients with patent foramen ovale: the Lausanne Study. Lausanne Stroke with Paradoxal Embolism Study Group. *Neurology* 1996;46:1301-1305.
38. De Castro S, Cartoni D, Fiorelli M, et al. Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke* 2000;31:2407-2413.
39. Zhu WX, Khandheria BK, Warnes CA, et al. Closure of patent foramen ovale for cryptogenic stroke in young patients: long-term follow-up. *Circulation* 1992;86:1-147.
40. Devuyst G, Bogousslavsky J, Ruchat P, et al. Prognosis after stroke followed by surgical closure of patent foramen ovale: a prospective follow-up study with brain MRI and simultaneous transesophageal and transcranial Doppler ultrasound. *Neurology* 1996;47:1162-1166.
41. Homma S, Di Tullio MR, Sacco RL, Sciacca RR, Smith C, Mohr JP. Surgical closure of patent foramen ovale in cryptogenic stroke patients. *Stroke* 1997;28:2376-2381.
42. Dearani JA, Ugurlu BS, Danielson GK, et al. Surgical patent foramen ovale closure for prevention of paradoxical embolism-related cerebrovascular ischemic events. *Circulation* 1999;100:II 171-II 175.
43. King TD, Thompson SL, Steiner C, Mills NL. Secundum atrial septal defect. Nonoperative closure during cardiac catheterization. *JAMA* 1976;235:2506-2509.
44. Rashkind WJ. Transcatheter treatment of congenital heart disease. *Circulation* 1983;67:711-716.
45. Sideris EB, Sideris SE, Fowlkes JP, Ehly RL, Smith JE, Gulde RE. Transvenous atrial septal defect occlusion in piglets with a "buttoned" double-disk device. *Circulation* 1990;81:312-318.
46. Babic UU, Grujicic S, Djurisic Z, Vucinic M. Transcatheter closure of atrial septal defects. *Lancet* 1990;336:566-567.
47. Pavcnik D, Wright KC, Wallace S. Monodisk:device for percutaneous transcatheter closure of cardiac septal defects. *Cardiovasc Intervent Radiol* 1993;16:308-312.
48. Das GS, Voss G, Jarvis G, Wyche K, Gunther R, Wilson RF. Experimental atrial septal defect closure with a new, transcatheter, self-centering device. *Circulation* 1993;88:1754-1764.
49. Sharafuddin MJ, Gu X, Titus JL, Urness M, Cervera-Ceballos JJ, Amplatz K. Transvenous closure of secundum atrial septal defects: preliminary results with a new self-expanding nitinol prosthesis in a swine model. *Circulation* 1997;95:2162-2168.
50. Windecker S, Meier B. Interventional PFO closure: what we see is but the tip of the iceberg. *Catheter Cardiovasc Interv* 2000;50:199-201.
51. Butera G, Bini MR, Chessa M, Bedogni F, Onofri M, Carminati M. Transcatheter closure of patent foramen ovale in patients with cryptogenic stroke. *Ital Heart J* 2001;2:115-118.
52. Dobrolet NC, Iskowitz S, Lopez L, Whalen R, Zahn EM. Sequential implantation of two Helex septal occluder devices in a patient with complex atrial septal anatomy. *Catheter Cardiovasc Interv* 2001;54: 242-246.

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