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. 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). 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 tranesophageal 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.
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. 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. Contrast echocardiography reveals that there is a clear prevalence of PFOs in adults who are <55 years with cryptogenic stroke, but not in the elderly. In a meta-analysis of case-control studies, the association between ischemic stroke and PFO was confirmed. 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

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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.

Patent foramen ovale (PFO)

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.

Figure 2: Embryogenesis of the interatrial septum.
motion towards the left or right atrium (Figure 4). The echocardiographic definition is exclusion 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 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.
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.43 Surgical closure is 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 occluder44 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 Device45 (Figure 7),
- Babic, the ASDOS Device,46
- Pavcnik, the Monodisk,47
- Das, the Angel-Wings Device, subsequently transformed into the Guardian Angel Device48 (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

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CVA = cerebrovascular accident; TIA = transient ischemic attack
Helex Device (Figure 7)\textsuperscript{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 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...
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 intro-
duced 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 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). 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

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**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)

**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.

<table>
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<th>Amplatzer PFO Occluder (n = 67)</th>
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\(P=0.006\)
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 evaluation of the advantages and disadvantages. It also seems acceptable to recommend closure to patients with a high risk of further events, (i.e., 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:

12. Cabanes L, Mas JL, Cohen A, et al. Atrial septal aneurysm and incomplete closure of a patent foramen ovale 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.

Bernhard Meier, M.D., Guest author, received his medical degree from the University of Zurich, Switzerland. He underwent training in internal medicine with board certification at the University Hospital of Zurich. There he participated as an assistant to Andreas R. Gruentzig in the world’s first percutaneous transluminal coronary angioplasty (PTCA) procedure on September 16, 1977. He has taken care of this patient since. After completing his cardiology training at Emory University in Atlanta, Georgia, he was appointed Chief of Invasive Cardiology at the University Hospital of Geneva, Switzerland, in 1983, and Professor of Cardiology at the University of Bern, Switzerland, in 1992 where he is currently holding the position of Chairman of the Cardiovascular Department, including cardiac surgery, vascular surgery, angiology, and cardiology. This department is the largest cardiovascular center in Switzerland.

Dr. Meier published the first comprehensive single-author book on PTCA in 1987. He has contributed to numerous other books and has published a large number of significant articles in the field of interventional cardiology. He has made contributions to the refinement and development of the techniques of PTCA, valvuloplasty, and percutaneous shunt closure. He has been a recipient of a number of awards and prizes and is regularly invited for educational activities in Switzerland and worldwide.