

The large patent foramen ovale

An underestimated cause of stroke

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Introduction

The atrial septum's oval fossa consists of an oval foramen with thick rims (limbus) closed by a flap valve (septum primum). It was probably designed on a Friday afternoon or Monday morning! It suffers from all the problems of a multifunctional device—in foetal life it has to provide a large interatrial communication, whereas in adult life it should be firmly shut. In the foetus it allows the more saturated returning umbilical venous blood to enter the left side of the heart from where it is pumped to the brain. After birth the higher left atrial pressure causes the flap to fall into position and functionally close the foramen ovale.

In most people, during the first few years of life, the upper edge of this flap valve sticks to the left atrial side of the foramen ovale to completely obliterate any possible interatrial communication. However, in about 25% of adults it remains patent. In most cases, this represents probe patency, such that a pathologists' probe or a cardiologists' catheter can barely be passed through. However, in a smaller percentage (1.3% in Hagen's post-mortem study had a patent foramen ovale (PFO) of 10mm or more) there is wider patency (pencil patency), in that a larger area of the flap valve is nonadherent to the limbus of the oval fossa, and a finger or inflated rubber balloon can be advanced backwards and forwards across the septum.

The flap valve can also be aneurysmal (defined as an excursion of the atrial septum of more than 10mm) with an incidence of 2 to 4% in healthy adults. Many of these aneurysms have an interatrial shunt with either patency in the region of the PFO or single or multiple holes in the aneurysm itself.

The flap valve can be markedly shorter than normal, resulting in a secundum atrial septal defect, which accounts for about 7% of congenital heart defects.

Pathogenesis

The PFO and aneurysmal interatrial septum are increasingly being incriminated in causing paradoxical cerebral and systemic thromboembolism (Figure 1). There is a very strong association between PFO and ischaemic stroke in younger patients, with a PFO being present in 54% of

patients with cryptogenic stroke. Although a quarter of adults have a patent foramen, most of these are probe patent and probably do not cause any harm, as they are both too small, and have a serpiginous course through the interatrial septum, to permit significant paradoxical thromboembolism. In contrast, large flap valve foramens are much more likely to allow significant paradoxical thromboembolism. A prospective study showed that, over a 21-month period of follow-up, patients with larger PFOs were more likely to have recurrent neurological events (5/16 vs. 0/18). It is difficult to prove with absolute certainty that a PFO allowed an embolus to pass across, unless the thrombus is actually seen crossing the PFO. There are quite a number of these “en flagrante” pictures in the literature. However, for the individual patient, treatment often has to be initiated on the assumption that the PFO allowed a venous thrombus to enter the left heart and hence the brain.

Attention also has to be paid as to why a thrombus formed in the first place. Deep vein thrombosis can be found in 10% of patients with PFO and stroke. Thrombophilic disorders (e.g. protein C or S deficiency) are commoner in this group of patients. Women with strokes on the oral anticoagulant pill have a high incidence of large PFOs. Some patients relate that the TIA occurred after a long-haul airline flight, which can cause deep vein thrombosis.

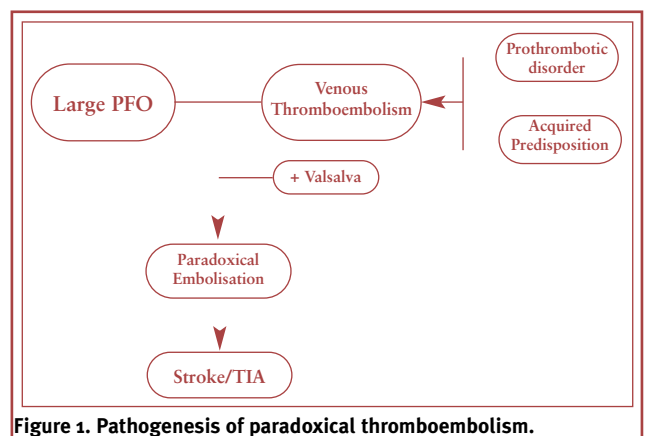


Figure 1. Pathogenesis of paradoxical thromboembolism.

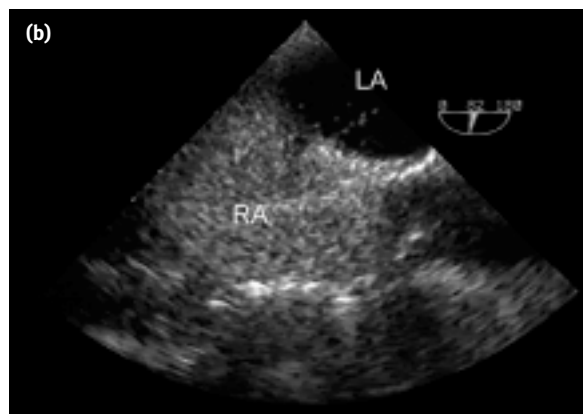
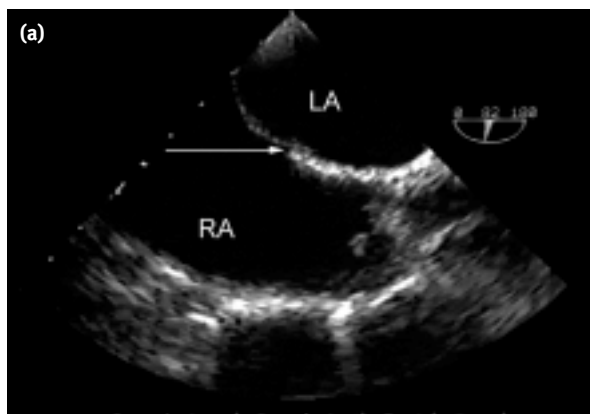


Figure 2. Transoesophageal echocardiogram showing (a) the flap valve PFO and micro-bubbles passing through it from right to left (b).

Identification of an atrial septal aneurysm or PFO in the absence of any events is not an indication for treatment. Burger et al. found that no CVAs occurred in 42 patients with atrial septal aneurysms followed for up to seven years.

Interestingly, patients with migraine with aura have a much higher incidence of PFOs. It has been suggested that the PFO allows the passage of platelet micro-emboli or serotonin into the left heart, which bypasses the lung's natural filtering role. Transcatheter closure of the PFO can reduce the frequency of their attacks.

Divers with neurological or cutaneous decompression illness after non-provocative dives have a very high incidence of large flap valve PFOs. The large PFO allows nitrogen bubbles formed during decompression to shunt from right to left. Transcatheter closure of the PFO prevents these divers developing this form of decompression illness.

Diagnosis

Comprehensive neurological evaluation and imaging to identify a cardio-embolic stroke has to be the first step. The history can sometimes be very helpful with the transient ischaemic attack/stroke occurring after a Valsalva type manoeuvre. Patients may have had central lines, pacemaker leads, Porta-caths etc., placed. Orthopaedic problems such as long-bone fractures and arthroplasties may result in fat embolism, which can occasionally traverse a large PFO.

Flap valve foramens are easy to demonstrate on contrast echocardiography with or without Valsalva manoeuvres. Patients with large flap valve foramens can be most easily recognised by the presence of a large right to left shunt at rest without provocative manoeuvres (Figure 2). In patients with small PFOs, it is possible for micro-bubbles to pass across such defects, but they are few in number and require repeated injections to demonstrate. Contrary to accepted wisdom, trans-thoracic echocardiography with six adequate contrast injections with and without Valsalva release is probably superior to transoesophageal echocardiography in detecting clinically relevant large PFOs. Trans-oesophageal echocardiography is used to assess the detailed anatomy of the PFO and also to exclude other cardiovascular sources of emboli.

Trans-cranial Doppler is another very useful technique, which tends to be underused for the diagnosis of large flap valve PFOs.

The PFO can also be assessed by cardiac catheterisation. Right atrial angiography shows that the defects relate to the lack of adherence of the septum primum to the superior part of the limbus of the oval fossa (Figure 4a). When they are balloon sized they stretch up to 10-24mm in diameter. Clearly balloon sizing and right atrial angiography will usually only be carried out at the time of planned transcatheter closure. However, if the defect was demonstrated to be only probe patent, then it is likely that device closure would not be helpful and that another cause was responsible for the symptoms.

Treatment

Treatment with anti-platelet agents (e.g. aspirin) or anticoagulants (warfarin) is usually recommended, although no randomised controlled or comparative trials have been performed. The annual risk of haemorrhage while on warfarin therapy is 1-2%. Furthermore, the recurrence rate of stroke and/or transient ischaemic attacks on medical treatment is 3-4%, which is similar to the risk of a patient with a high-grade carotid artery stenosis or with atrial fibrillation.

Surgical PFO closure is an option, but there is relatively little clinical experience with this form of treatment. Furthermore, in the era of trans-catheter occlusion, surgical closure of the PFO on cardiopulmonary bypass is very unlikely to be recommended or undertaken.

Transcatheter closure of the PFO to prevent paradoxical embolism using the clamshell device, the adjustable buttoned

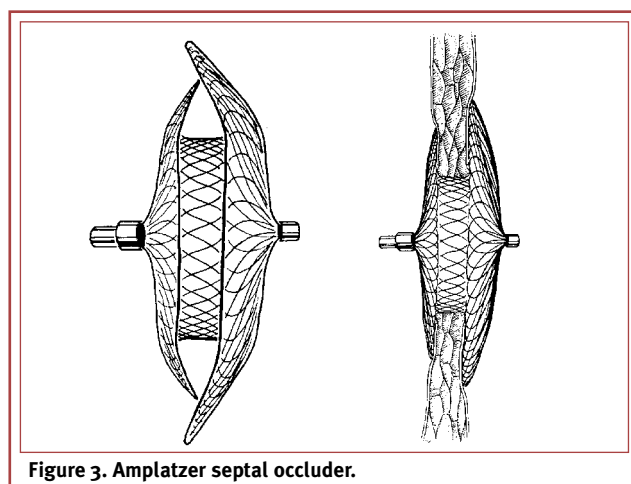


Figure 3. Amplatzer septal occluder.

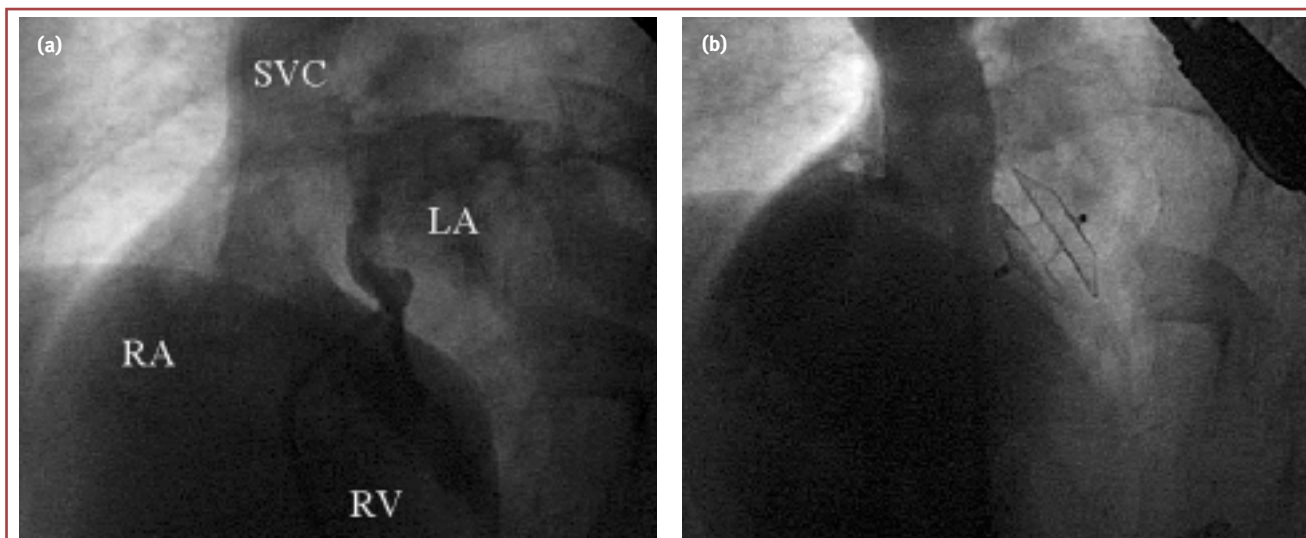


Figure 4. PFO closure with an 11mm Amplatzer septal occluder.
(a) Right atrial angiogram shows the injected contrast pushing the flap valve open and the contrast shunting into the left atrium.
(b) After placement and release of the device the PFO is sealed by the stenting mechanism of the device.

device, or the Amplatzer septal or patent foramen occluder has been available for a number of years. The procedure is technically simple and can be performed as a day case. The device most commonly used is the Amplatzer septal occluder (Figure 3), which is made from a nitinol wire mesh that is heat shaped into a double disk device, which contains polyester patches. The Amplatzer septal occluders have a central connecting waist that serves to stent the defect, thereby producing occlusion. The PFO occluders have no central waist and the disks hold the flap valve against the limbus. Nitinol is a memory metal and the devices can be compressed and introduced into a vascular sheath already positioned across the defect. Once the device is pushed out of the end of the sheath the first disk reforms and can be pulled onto the left side of the atrial septum under X-ray screening. The second disk is then deployed on the right side of the septum by pulling back the sheath. The alignment of the device with the septum is checked on trans-oesophageal echo and the device is then released by unscrewing it from its delivery cable (Figure 4). Patients are usually given aspirin and clopidogrel for six months after the implant. Possible complications consist of: device migration (<1% and probably related to learning curve effects); cerebral thromboembolism (0.3%); arrhythmia (2% particularly if there was pre-existing supraventricular tachycardia). Severe or life threatening complications (e.g. cardiac tamponade, septicaemia) should be exceedingly rare.

In one study of 281 transcatheter PFO closures, freedom from recurrence of TIA, ischaemic stroke and peripheral embolism was 94.1% at three years with all recurrent events occurring in patients implanted with the older device designs. Recurrent neurological events (3.4%) may also be related to closing “bystander” PFOs in patients with as yet undetected other causes. Randomised controlled trials comparing device closure with medical treatment are currently

underway, but it will be a number of years before the results are available. In the meantime, what should we do with the patient with a cryptogenic stroke and a PFO? In those patients with a large flap valve PFO or atrial septal aneurysm transcatheter closure should be considered, bearing in mind the incomplete evidence base. A thrombophilic tendency should be extensively searched for, as these patients will need modified anticoagulant/antiplatelet protocols after transcatheter closure.

Summary

- Paradoxical embolism through a PFO is now a well-known cause of stroke.
- Comprehensive neurological and cardiological evaluation and imaging is required to identify such patients.
- The reason for the formation of the thrombus should also be searched for.
- Transcatheter closure of the PFO is a feasible therapeutic option.
- Prospective randomised controlled trials comparing medical and catheter closure are underway; however the results will not be known for several years.
- In the meantime, transcatheter closure can be considered for patients with a large flap valve PFO or atrial septal aneurysm who have had, or who are at risk of recurrent events.

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