Editorial

How should patients with patent foramen ovale be managed?

The development of percutaneous devices capable of closing atrial septal defects has led to renewed debate about optimal management of patients with patent foramen ovale (PFO). Echocardiography has made diagnosing PFO routine, but in most patients appropriate management, including the role of device closure, remains a matter of speculation.

**Anatomy and prevalence**

During infancy, fibrous adhesions usually seal the atrial septum, but occasionally it does not seal completely, giving rise to a patent foramen ovale (PFO). In some individuals, excess atrial septal tissue in the region of the fossa ovalis causes increased movement of the septum during respiration. When excursion is greater than 10 mm this appearance is classified as an atrial septal “aneurysm”, which can occur in isolation, or in combination with a PFO.1

PFO is a common finding in the normal healthy population. A necropsy study of 965 normal human hearts showed an overall prevalence of 27%, with no sex differences, and a mean PFO diameter of 5 mm.2 Small PFO probably close spontaneously throughout adult life, as there is a reduction in prevalence from 34% in the first three decades compared to 20% in the ninth and tenth decades.2 Observational echocardiography studies have identified atrial septal aneurysm in about 2–4% of the normal population,3,4 associated with a PFO in up to 70% of cases.5

**Diagnosis**

Transoesophageal echocardiography (TOE) is the investigation of choice for the diagnosis of PFO. Even if the interatrial septum looks normal on two dimensional imaging, colour Doppler may show flow between the atra. Sensitivity is improved by Valsalva and coughing manoeuvres, which transiently increase right atrial pressures, with injection of microbubble contrast agents (agitated saline or gelatine). Passage of microbubbles from right to left atrium within three cardiac cycles usually identifies a PFO. Size is graded as small (up to 5 bubbles), medium (6–25 bubbles) or large (≥ 25 bubbles).6,7 Together, colour Doppler and contrast TOE have a high sensitivity and specificity for the diagnosis of PFO.7,8

Transthoracic echocardiography (TTE) with contrast injection can be used to diagnose PFO, but has a sensitivity of up to 80% compared to TOE.8 Thus, a negative TTE does not exclude a PFO, but a diagnostic TTE may avoid the need for a TOE.

Transcranial Doppler sonography after contrast injection is used extensively in anaesthetics, neurology, and vascular surgery for identifying patients with PFO. Characteristic high pitched Doppler signals detected over the middle cerebral artery identify a shunt and sensitivity is increased by the Valsalva manoeuvre. Transcranial Doppler appears to have a similar sensitivity and specificity to TOE for the diagnosis of PFO.9-11 However, in one study 4/44 patients with abnormal transcranial Doppler responses had no evidence of a cardiac shunt on TOE.11 This discrepancy was attributed to the patients performing a more complete Valsalva manoeuvre in the absence of sedation.

**Consequences of PFO**

Although PFO is common, adverse consequences arise infrequently. However, when right atrial pressure is increased, right to left interatrial shunting can occur, and deoxygenated blood or emboli (“paradoxical embolism”) may enter the systemic circulation. Such changes may occur transiently—for example, during sneezing9 or during “Valsalva” manoeuvres such as weightlifting.10 Right to left shunting may persist in cases of right ventricular myocardial infarction11 (leading to hypoxemia), structural tricuspid valve disease,12 or more commonly following acute pulmonary embolism.13 In patients with major pulmonary embolism, PFO is associated with a worse prognosis,14 and it has been suggested that screening for PFO should be performed in such cases, to help target aggressive treatment.22

PFO with significant right to left shunting may have a role in the pathogenesis of decompression illness following sub-aqua dives. It is hypothesised that venous gas bubbles liberated after the diver’s rise to the surface may enter the systemic circulation through a PFO and embolise into the central nervous system (CNS).22 However, although many divers may have a PFO, few dives are complicated by decompression illness,23 and other factors, including pulmonary barotrauma and the CNS response to ischaemic injury, may contribute to the clinical syndrome.24

PFO has been implicated in the pathogenesis of arterial thromboembolism. Direct evidence for this comes from more than 30 case reports of impending paradoxical embolism, in which thrombus was visualised in transit through a PFO.22 Most of these cases presented with acute pulmonary embolism, and systemic arterial embolisation involving limbs, viscera, coronary arteries, or the cerebral circulation.

However, in most patients with possible embolic disease, trans-septal thrombus is not visualised by cardiac imaging. Determining whether paradoxical embolism has occurred through a PFO ideally requires documentation of a “triad” of the PFO, raised right atrial pressure, and a venous source of thrombus. Unfortunately documenting the components of this triad is difficult; venous thrombus was identified in only 10% of patients with PFO and stroke,8 and can be proven in only 50% of cases of definite pulmonary embolism.25 This inability to exclude venous thrombosis has maintained interest in the potentially pathological role of PFO, particularly among young adults with strokes that are unexplained (or “cryptogenic”) despite extensive investigation.26

Numerous investigators have reported an association between PFO and ischaemic stroke in younger patients.4,5,10,27 One retrospective study demonstrated a higher prevalence of PFO in stroke patients than in age matched controls (40% vs 10%), and higher still (54%) in 26 patients with cryptogenic stroke.27 A case–control study of patients with cryptogenic stroke used stepwise logistic
regression analysis to calculate a stroke odds ratio of 3.0 (95% confidence interval (CI) 1.1 to 8.1) for a patient with PFO, an odds ratio of 2.1 (95% CI 0.4 to 10.4) for a patient with atrial septal aneurysm alone, and an odds ratio of 33.3 (95% CI 4.1 to 270) for a patient with both these abnormalities. However, contrasting data from a recent prospective study of 42 patients in whom atrial septal aneurysm was identified incidentally (56% with associated PFO), revealed no cerebrovascular events over a mean follow-up period of 5.8 years (range 4.7–7.1 years).29

Data supporting a pathological role for PFO in cryptogenic stroke have also come from cerebral imaging. A retrospective analysis showed “embolic-type” cerebral infarcts were more likely in patients with larger PFO (more than 2 mm diameter).30 However, these 95 patients were heterogeneous and patients with a clearly determined cause of stroke had not been excluded.

A single prospective study has demonstrated a correlation between the size of the interatrial shunt and risk of ischaemic stroke.31 Patients were divided into two groups and over 21 months follow up, 5/16 patients (mean age 58 years) with large shunts had recurrent neurological events, compared with 0/18 patients (mean age 54 years) with smaller shunts (p = 0.03). These events occurred despite antplatelet or anticoagulant treatment. The definition of a large shunt in this series was detection of more than 20 bubbles in a single video frame without provocative manoeuvres.

Treatment

Management options include aspirin or warfarin, or both, and closure of the PFO either by open surgery or by percutaneous catheter based devices. There have been no prospective randomised trials of these treatments and published event rates in uncontrolled series vary considerably (table 1).

Limited data exist on recurrent event rates in young stroke patients with PFO treated medically. In a retrospective study of aspirin or warfarin treatment, 0/69 patients with PFO alone, 1/25 patients with isolated atrial septal aneurysm, and 5/38 patients with both abnormalities had a recurrent stroke or transient ischaemic attack (TIA) during a two year period.32 A similar study of 140 patients with PFO followed for a mean of three years reported a recurrent stroke rate of 1.9% per annum.33 However, in both of these studies event numbers were too small to differentiate between treatments, and subclinical ischaemic events could have been missed.

Data on long term outcome following surgical PFO closure is limited to small uncontrolled case series.34–36 Follow up ranged from seven months to four years, and pharmacological treatment was not controlled, but included aspirin or warfarin in about half the patients. No operative complications were reported and the recurrent event rate varied from 0%36 to 19.3%.35 A recent retrospective analysis of 91 patients who had surgical closure of a PFO following a cerebral infarct reported a recurrent TIA rate of 16% over four years, despite TOE demonstration of an intact repair in each case.36

More recently, catheter based devices have been used to close atrial septal defects (ASD) and PFO. A multicentred observational study using a double umbrella type closure system in 154 consecutive patients with ASD and in 46 patients with PFO reported procedure failure in 26 patients, and subsequent surgical removal of the device in a further 12 patients.37 During a mean follow up of 17 months, 1/46 patients with PFO had a recurrent neurological event. Improved procedural results were obtained with a different self expanding double disk device (Amplatzer septal occluder) in 100 consecutive patients (seven with PFO).40 Deployment failures occurred in only seven cases, with one device embolisation, and four other complications, including a probable TIA. However, by follow up at three months, 92/93 successfully treated defects remained closed. A recent prospective but uncontrolled study of percutaneous PFO closures in 80 cryptogenic stroke patients using various devices reported a procedural success rate of 98%, with a 10% complication rate (including cardiac tamponade, air embolisation and device embolisation).38 However, a residual interatrial shunt was detected by TOE in 21/78 patients, and over a mean follow up of 1.6 years (range 0.1–5 years) the average annual recurrent thromboembolic event rate was 3.4%. Of the eight patients with recurrent events, three had no evidence of a residual shunt.

Conclusions

PFO is common enough in the normal population to be considered an anatomical variant, and for any individual the absolute risk of adverse events from a PFO is clearly very small. When right atrial pressure is increased, right to left shunting is possible, and this may exacerbate hypoxae mia in pulmonary embolism and right ventricular infarction. There are also data to suggest PFO may have a role in decompression illness in divers.

When venous thrombosis coexists with raised right atrial pressure, paradoxical embolism through a PFO can occur, and this may result in stroke or peripheral arterial emboli. However, in most cases of cryptogenic stroke with PFO there is no definite evidence of paradoxical embolism. In these cases, percutaneous or surgical PFO closure to prevent recurrent thromboembolic events is not a proven strategy, as event rates following intervention appear similar to those achieved with medical treatment, and there is an additional procedural risk.

It seems likely that within the population of patients with PFO and embolism there are further mechanisms, such as occult clotting abnormalities, which may be responsible for recurrent events. At present, closure of large PFO in patients with cryptogenic stroke (passage of more than 20 microbubbles without provocative manoeuvres) appears to be reasonable if recurrent symptoms occur despite optimal medical treatment, or if all the elements of the triad necessary for paradoxical embolism (PFO, venous thrombosis, and increased right heart pressures) are clearly documented. But patients undergoing closure of PFO should be warned that even despite apparently successful intervention, their risk of recurrent events remains elevated and that medical treatment should probably be continued lifelong.

Table 1  Recurrent thromboembolic event rates with different patent foramen ovale (PFO) management strategies

<table>
<thead>
<tr>
<th>Management strategy</th>
<th>Annual recurrent event rate</th>
<th>References</th>
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<tbody>
<tr>
<td>Aspirin or warfarin</td>
<td>1.9–14%</td>
<td>Stone et al31</td>
</tr>
<tr>
<td>Surgical PFO closure</td>
<td>0–19.5%</td>
<td>Homma et al44</td>
</tr>
<tr>
<td>Percutaneous PFO closure</td>
<td>3.4%</td>
<td>Windenker et al45</td>
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Dearani et al31
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Mas and Zuber35
Bogousslavsky et al43

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