Holes and strokes

MUSHTAQ WANI, RANJINI NAVARATNASINGAM

Abstract

Five case histories are described to illustrate the importance of patent foramen ovale and atrial septal aneurysm as risk factors in stroke aetiology. Diagnostic methods, and the current and future management of these atrial septal defects, are briefly discussed.

Key words: stroke, risk, recurrence, patent foramen ovale (PFO), atrial septal aneurysm (ASA), transthoracic echocardiogram (TTE), transoesophageal echocardiogram (TOE).

Br J Cardiol 2005;**12**:53–6

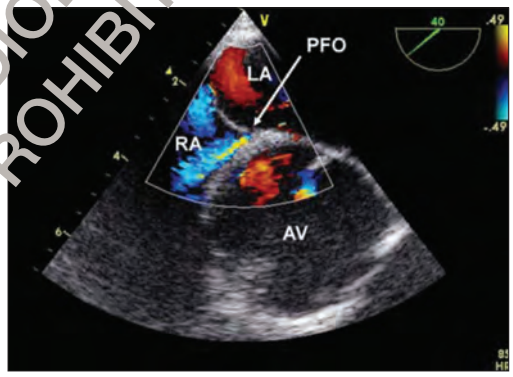
Case history 1

A 37-year-old woman, on holiday in Italy, developed a sudden headache while she was in the swimming pool. On coming out, she noticed weakness of her left arm and leg. She was admitted to hospital where a left hemiparesis was confirmed. She also had global aphasia. Initial CT scanning of the head on the day of admission was normal but a repeat head CT three days later showed a right parietal infarct. A Doppler ultrasound of her legs revealed thromboses in the left superficial femoral and popliteal veins. An electrocardiogram (ECG) and transthoracic echocardiogram (TTE) were normal. However, a transoesophageal echocardiogram (TOE) showed a patent foramen ovale (PFO) (figure 1).

She had no significant past medical history except migraine. She did not use the oral contraceptive pill (OCP). However, she did have marginally raised serum fibrinogen (410 mg/dL; normal range = 170–400 mg/dL) and her mother had a history of deep venous thrombosis. On her return to the UK, a repeat contrast TOE performed at her local hospital confirmed a PFO with a moderate degree of right to left shunt (spontaneous and Valsalva-induced contrast). The erythrocyte sedimentation rate (ESR), plasma viscosity, fibrinogen, proteins C and S, antithrombin III and anticardiolipin antibodies were normal. Clotting studies were not performed since she was taking calcium heparin and aspirin, which were then changed to warfarin. After a period of rehabilitation, she went home independently mobile and able to care for herself. She had her PFO closed using a percutaneous transvenous catheter approach and her anticoagulation was stopped three months later.

Department of Stroke Medicine, Swansea NHS Trust, Morriston Hospital, Morriston, Swansea, SA6 6NL.
Mushtaq Wani, Consultant Physician
Ranjini Navaratnasingam, Staff Grade Doctor
Correspondence to: Dr M Wani
(email: mushtaq.wani@swansea-tr.wales.nhs.uk)

Figure 1. Transoesophageal echocardiogram showing patent foramen ovale, separation of two interatrial septal flaps and right to left shunt



Case 2

A 32-year-old woman developed numbness of her face while having a wash. She fell, and noticed weakness of her right side. She had no risk factors for cerebrovascular disease or thromboembolism other than use of the OCP. A CT scan of the head showed ischaemia in the left middle cerebral artery (MCA) territory. The ESR, clotting screen and autoantibodies, including antiphospholipid antibodies, were normal. The ECG, leg and carotid Doppler and TTE were all normal. However, TOE showed a PFO and an atrial septal aneurysm (ASA) (figure 2). She was treated with warfarin, and made a very good recovery. Her PFO was closed, ASA was repaired and her anticoagulants were stopped three months later.

Case 3

A 37-year-old man presented with right hemiparesis. A CT scan of the head showed an infarct in left MCA territory. Carotid Doppler showed a clot occluding the left internal carotid artery (ICA). A Doppler of the legs showed bilateral clots. TOE showed a PFO, with a right to left shunt. However, since he could not per-

Figure 2. Transoesophageal echocardiogram showing patent foramen ovale and interatrial septum aneurysm with right to left shunt

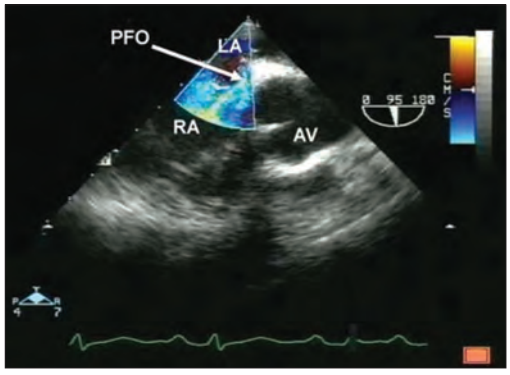
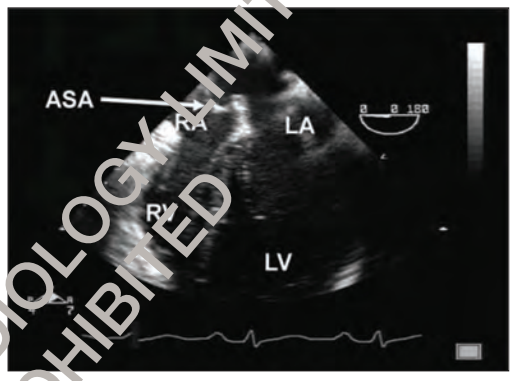


Figure 3. Transoesophageal echocardiogram showing interatrial septum aneurysm



form the Valsalva manoeuvre the magnitude of the shunt could not be quantified at that time. He is on warfarin, awaiting further assessment of his PFO.

Case 4

A 58-year-old non-smoker with no classic risk factors for atherosclerosis presented to his optician with left upper quadrantanopia. CT of the head showed an ischaemic infarct in the right temporal area. His right calf looked pigmented as a result of a deep venous thrombosis (DVT) about 30 years before, following an appendicectomy. In view of this he had Doppler of the leg performed, but this was negative for clots. Carotid Doppler did not show any significant stenosis. A TOE showed a PFO with a mild right to left shunt. He was prescribed long-term aspirin.

Case 5

A 66-year-old woman was admitted with an inferior myocardial infarction (MI). She had a history of hypertension and smoked cigarettes. Two days after admission she developed expressive dysphasia and right arm weakness. CT of the head showed a left parietal infarct. A TTE showed a small PFO and reduced left ventricular function. The findings were confirmed with TOE. Although a left ventricular thrombus could possibly have contributed to stroke, in view of her risk factors carotid Doppler was carried out. This showed critical stenosis of the left carotid artery. She was referred for urgent carotid endarterectomy.

Discussion

Prevalence of patent foramen ovale

Paradoxical embolism through a patent foramen ovale is well known.[1] Embolism to the lungs,[2] ophthalmic and coronary arteries and other peripheral vessels has been reported. Autopsy studies have shown a prevalence of PFO of between 20% and 35% among the normal population.[3] An increased prevalence has been reported in the brains of divers.[4,5] It has also been suggested that PFO might be a family trait in women.[6]

PFO and stroke

The role of PFO as a risk factor for ischaemic stroke has been debated for many years. However, recent studies have gathered more substantial evidence to incriminate PFO and atrial septal aneurysm (ASA) as risk factors for ischaemic stroke, especially in the young.[7-10] Echocardiographic studies have shown a PFO prevalence of 26% in cryptogenic stroke (no known risk factors), 14% in stroke with one risk factor and 3.2% in normal controls. Thus, cryptogenic stroke patients are about eight times more likely to have a PFO than the general population.[10] Cases 1 and 2 prove beyond doubt that PFO is an important factor in the mechanism of embolisation. Air travel[11-13] and the Valsalva manoeuvre were other important risk factors in case 1.

Contrast TOE has shown a significantly higher prevalence of PFO in cryptogenic (no obvious risk factor) strokes, especially in the young.[1,14] Some studies have shown no increase in prevalence of PFO in the elderly.[15] However, some researchers argue that older people are less likely to be investigated for PFO since most will have classic risk factors for atherosclerosis, as illustrated by our case 5.[10]

Risk of stroke recurrence

People with PFO who have had an ischaemic stroke are at risk of having further strokes. A meta-analysis showed a five-fold risk for recurrent events in the presence of a PFO. The risk is even higher if an ASA is also present.[16] Other studies have shown no significant risk with isolated PFO but a high risk in association with ASA.[17] Factors associated with higher recurrence are size of PFO (> 5 mm), severity of right to left shunt (> 50% left atrium filling),[18-20] spontaneous echo contrast, > 20 microbubbles, posterior cerebral artery infarct, recent active migraine and presence of an ASA.[21] Some investigators have identified other morpho-

Key messages

- Paradoxical embolism through a patent foramen ovale (PFO) is well known
- PFO is becoming increasingly recognised as a risk factor for ischaemic stroke (especially cryptogenic)
- Atrial septal aneurysm (ASA) seems to be a risk factor only in association with a PFO
- Contrast transoesophageal echocardiography is the best investigation to assess the presence and severity of PFO and ASA
- Although percutaneous closure of PFO and repair of ASA seem promising in terms of effectiveness and safety, large prospective studies are urgently needed to compare this with surgical repair and antithrombotic therapy

logical features, such as Eustachian valve directed toward the PFO, as further risk factors.[22] Other factors, such as a hypercoagulable state, put some patients with a PFO at higher risk than others.

Atrial septal aneurysm

An ASA or a hypermobile septum primum in isolation (figure 3) or in association with PFO (figure 2) has been considered to confer higher risk for ischaemic stroke.[23] However, a large study involving 600 patients and four-year follow-up showed no risk associated with an ASA unless a PFO was also present.[24] ASA is now generally accepted as a risk factor only in the presence of a co-existing PFO.[25,26]

Diagnosis

Contrast TOE, especially with Valsalva manoeuvre, is the best investigation to detect the presence of PFO and its severity.[1,14,17-20] Recently, transcranial Doppler ultrasound is also proving a reliable and sensitive test.[27,28]

Source of embolus

Whereas a peripheral venous site seems the most likely origin for paradoxical embolisation in patients with a PFO, in-situ thrombus formation is thought to be the likely source in patients with an ASA. In most cases, the venous source of clots cannot be established (cases 2 and 4). Even when such clots are detected, their significance may be uncertain (cases 1 and 3). Studies have shown a prevalence of between 10%[29] and 57%[30] in patients with suspected paradoxical embolism.

Management

Management of strokes associated with a patent foramen ovale or atrial septal aneurysm has been non-evidence based. High annual recurrence after a stroke or a transient ischaemic attack seems to be the logical reason for the treatment of PFO.[16] However, there is no consensus on whether to treat PFO surgically (by direct or percutaneous transcatheter closure) or medically (using antiplatelet or anticoagulant therapy).[31,32] The Lausanne study showed an 8% recurrence rate in patients treated surgically, 26% recurrence in those treated with anticoagulants and 66% recurrence in those treated with antiplatelet therapy.[33] Good results have been seen in selected centres after surgical closure.[34] Percutaneous closure of PFO and repair of ASA seems to be a very promising approach.[35] However, studies involving surgery or catheter closure have been either too small or retrospective. There is an urgent need for prospective studies to compare percutaneous closure, surgical repair and antithrombotic therapy.

Conflict of interest

None declared.

References

1. Hausmann D, Mugge A, Becht I, Daniel WG. Diagnosis of patent foramen ovale by transoesophageal echocardiography and association with cerebral and peripheral embolic events. *Am J Cardiol* 1992;**70**:668-72.
2. Konstantinides S, Geibel A, Kasper W *et al*. Patent foramen ovale is an important predictor of adverse outcome in patients with major pulmonary embolism. *Circulation* 1998;**97**:1946-51.
3. Hagen PT, Scholz DG, Edwards JE. 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.
4. Knauth M, Ries S, Pohiman S *et al*. Cohort study of multiple brain lesions in sport divers; role of a patent foramen ovale. *BMJ* 1997;**314**:701-05.
5. Schwerzmann M, Seiler C, Lipp E *et al*. Relation between directly detected foramen ovale and ischaemic brain lesions in sport divers. *Ann Intern Med* 2001;**134**:21-4.
6. Arquizan C, Coste J, Touboul P-J, Mas J-L. Is patent foramen ovale a family trait? A transcranial doppler monographic study. *Stroke* 2001;**32**:1563-6.
7. Mass JL. Patent foramen ovale, atrial septal aneurysm and ischaemic stroke in young adults. *Eur Heart J* 1994;**15**:446-9.
8. Lechat P, Mass JL, Lascault G *et al*. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988;**318**:1148-52.
9. Windecker S, Meier B. Patent foramen ovale and atrial septal aneurysm: when and how should they be treated. *ACC Curr J Rev* 2002;**11**:97-101.
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**:1316-20.
11. Giangrande PLF. Air travel and thrombosis. *Int J Clin Pract* 2001;**55**:690-3.
12. Scurr JH, Machi S, Bailley-King S, Mackie IJ, McDonald S, Smit PDC. Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights; a randomised trial. *Lancet* 2001;**357**:1485-9.
13. Belcaro G, Geroulakos G, Nicolaides A, Myers KA, Winford M. Venous thromboembolism from air travel; The LONFLIT Study. *Angiology* 2001;**52**:369-74.
14. Webester MWI, Chancellor AM, Smith HJ, Swift DL, Sharpe DN, Bass NM. Patent foramen ovale in young stroke patients. *Lancet* 1988;**2**:11-12.
15. Jones EF, Calafiore P, Donnan GA, Tonkin AM. Evidence that patent foramen ovale is not a risk factor for cerebral ischaemia in the elderly. *Am J Cardiol* 1994;**74**:596-9.
16. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000;**55**:1172-9.
17. Homma S, Sacco RL, di Tullio MR *et al*. Effect of medical treatment in stroke patients with patent foramen ovale; Patent Foramen Ovale in Cryptogenic Stroke Study. *Circulation* 2002;**105**:2625-31.
18. Hausmann D, Mugge A, Daniel WG. Identification of patent foramen

ovale permitting paradoxic embolism. *J Am Coll Cardiol* 1995;**26**:1030-8.
19. Comess KA, de Rook FA, Beach KW, Lytle NJ, Golby AJ, Albers GW. Transoesophageal echocardiography and carotid ultrasound in patients with cerebral ischaemia: Prevalence of findings and recurrent strike risk. *J Am Coll Cardiol* 1994;**23**:1598-603.
20. Stone DA, Godard J, Correlti MC *et al*. Patent foramen ovale: Association between the degree of shunt by contrast transoesophageal echocardiography and the risk of future ischaemic neurological events. *Am Heart J* 1996;**131**:158-61.
21. Bogousslavsky J, Garazi S, Jeanrenaud X, Aebischer N, Van Melle G, for the Lausanne Stroke Registry Group: Stroke recurrence in patients with patent foramen ovale. *Neurol* 1996;**46**:1301-05.
22. Homma S, Sacco RL, Di Tullio MR *et al*. Characteristics of patent foramen ovale associated with cryptogenic stroke: a biplane transoesophageal echocardiographic study. *Stroke* 1994;**25**:582-6.
23. Yoram A, Khandheria BK, Meisser I *et al*. Frequency of atrial septal aneurysm in patients with cerebral ischaemic events. *Circulation* 1999; **99**:1942-4.
24. Mas JL, Arquiza C, Lamy C *et al*. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm or both. *N Engl J Med* 2001;**345**:1740-6.
25. Cabanes L, Mass 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 transoesophageal echocardiography. *Stroke* 1993;**24**:1565-73.
26. Mass JL, Zuber M. Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient Ischaemic attack. French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. *Am Heart J* 1995;**130**:1083-8.
27. Ley-Pozo J, Ringelstein EB. Non-invasive detection of occlusive disease of the carotid siphon and middle cerebral artery *Ann Neurol* 1990;**28**:640-7.
28. Di Tullio M, Sacco RL, Venketasubramanian N *et al*. Comparison of diagnostic techniques for the detection of a patent foramen ovale in stroke patients. *Stroke* 1993;**24**:1020-4.
29. Lethen H, Flachskampf FA, Schneider R *et al*. Frequency of deep venous thrombosis in patients with patent foramen ovale and ischaemic stroke or transient ischaemic attack. *Am J Cardiol* 1997;**80**:1066-9.
30. Stöllberger C, Slany J, Schuster I, Leitner H, Winkler W-B, Karnik R. The prevalence of deep venous thrombosis in patients with suspected paradoxical embolism. *Ann Intern Med* 1993;**119**:461-5.
31. Nendaz M, Sarasin FP, Bogousslavsky J. How to prevent stroke recurrences in patients with patent foramen ovale: anticoagulants, antiaggregants, foramen closure or nothing? *Eur Neurol* 1997;**37**:199-204.
32. Sacco R, Di Tullio MR, Homma S. Treatment of foramen ovale and stroke: to close or not to close, that is not yet the question. *Eur Neurol* 1997; **37**:200-06.
33. Devuyst G, Bogousslavasky J, Ruchat P *et al*. Prognosis after stroke followed up by surgical closure of patent foramen ovale; A prospective follow-up study with brain MRI and simultaneous transoesophageal echocardiography and transcranial Doppler ultrasound. *Neurol* 1996;**47**:1162-6.
34. 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**:2376-81.
35. Windecker S, Wahl A, Chaterjee T *et al.* Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: Long term risk of recurrent thromboembolic events. *Circulation* 2000;**101**:893-8.

Correction

Please note that this is a corrected version of the primary article that was originally published, which unfortunately contained some incorrect figures. The authors and editors apologise for the mistake.