Modern management of a patent foramen ovale

G S Kanaganayagam • I S Malik

Hammersmith Hospital, Cardiovascular Sciences and the Renal Institute, Imperial College London and Imperial College Healthcare NHS Trust, London, UK

Correspondence: Iqbal Malik. Email: iqbal.malik@imperial.nhs.uk.

DECLARATIONS

Competing interests
ISM has been involved in PFO trials in Migraine and Stroke

Funding
None

Ethical approval
None required

Guarantor
ISM

Contributorship
ISM provided the framework for the article and GSK wrote the preliminary draft of the article, which was then reviewed and amended by ISM

Acknowledgements
None

Summary

A patent foramen ovale (PFO) has been associated with medical conditions such as cryptogenic stroke, migraine with aura, and decompression illness. Whether closure of the PFO has clinical benefit has been suggested from registry studies, but not yet confirmed in multiple randomized trials. Methods of diagnosis of a PFO and a summary of the current evidence for treatment is presented and discussed as a guide to patient-centred decision-making.

Introduction

What is a patent foramen ovale?

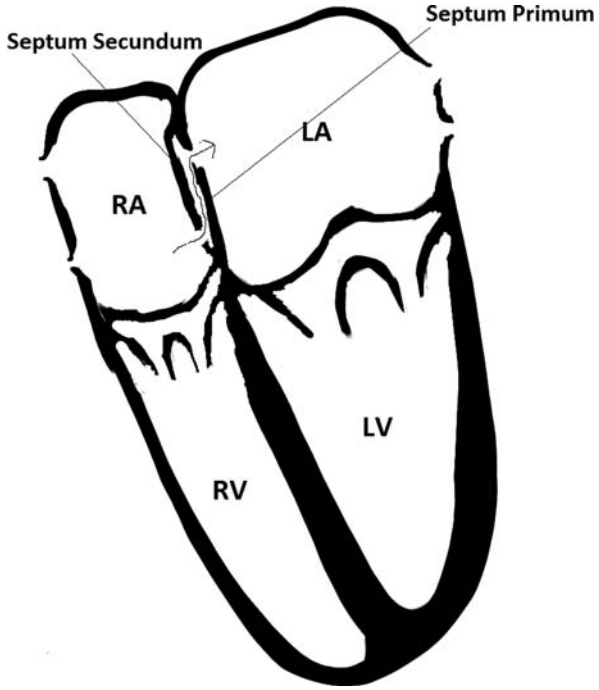
The foramen ovale is an inter-atrial slit within the septum secundum serving as a conduit between the right and left atria. During development, oxygenated blood is received via the umbilical cord and directed into the right atrium, where the majority passes through the foramen ovale into the left atrium, on to the left ventricle and through to the rest of the developing fetus. A small fraction of the blood continues from the right atrium into the right ventricle, through the pulmonary artery and then via the ductus arteriosus (another fetal conduit that closes soon after birth) into the aorta, avoiding the redundant fetal lungs. During the first breath, as the lungs expand, the resistance in the pulmonary circulation drops and the pressure difference between the left and right atria increases causing physiological closure of the hole as the left-sided septum primum is forced against the slit in the septum secundum. The flap itself usually seals to the surrounding fossa ovalis by the end of the first year of life. Thus, a foramen ovale is patent when this anatomical closure does not occur, as found in up to 25% of the adult population (Figure 1).[1] This persistent communication could allow deoxygenated blood and emboli to pass paradoxically from the right to left-sided circulation. A patent foramen ovale (PFO) is anatomically different from an atrial septal defect, which represents malformation of the septum primum, septum secundum and/or sinus venosus.

How do you diagnose a PFO?

Transcranial Doppler

Transcranial Doppler (TCD) is used to study flow patterns in the middle cerebral artery following peripheral intravenous injection of agitated saline. The method involves bi-temporal monitoring of the middle cerebral arteries with a 2 MHz probe for the appearance of air bubbles during normal respiration and manoeuvres such as sniff and Valsalva. These manoeuvres lead to an increase in intrathoracic pressure, a reduction in systemic venous return, a subsequent decrease in pulmonary circulation and a drop in left atrial pressure, temporarily reversing the pressure difference between the left and right atria.[2] The optimal timing of injection of contrast is before Valsalva manoeuvre allowing time for bubbles to accumulate by the release phase of the Valsalva, at which point the pressure gradient between the

Figure 1
The hole in the septum primum is the ostium secundum and the surrounding area beneath the hole in the septum secundum is the fossa ovalis. These two gaps allow inter-atrial communication through the passage known as the foramen ovale (arrow)



right and left atria are at a maximum.[3] TCD with contrast has shown greater sensitivity than transthoracic echocardiography (TTE) with contrast at identifying PFO.[4] The sensitivity of the procedure is offset by the lack of specificity as it identifies any shunt including atrial and/or ventricular-septal defects, intrapulmonary shunts and any arteriovenous malformation. In addition, many of the indications for identification of a PFO involve a differential diagnosis of intracardiac thrombus, which is not identified using TCD.

Transthoracic echocardiography

TTE can infrequently identify a PFO using colour Doppler flow. However, if a PFO is suspected, a TTE should be performed with contrast (a mixture of gelofusin + air, or saline + blood injected as a bolus). A PFO is confirmed if contrast appears in the left atrium within three cardiac cycles from opacification of the right atrium. The size of the shunt can also be approximated by assessing the number of bubbles seen. The same respiratory and provocative manoeuvres as for TCD are used. A protocol with one resting injection, injections during three Valasalva's and two sniffs effectively excludes a significant PFO.[5] Harmonic imaging has been shown to improve sensitivity of TTE and more recently 3D TTE has been shown to be similar to transoesophageal echocardiography (TOE) with contrast and significantly better than TTE with contrast in identification of a PFO.[6]

Transoesophageal echocardiography

The inter-atrial septum is closer to the probe using TOE and, therefore, the exact anatomy is visualized more clearly; the disadvantage is that it is more invasive and it can be difficult for the patient to perform a Valsalva manoeuvre, which may cause a false negative result. The optimal choice is largely centre or physician dependent, with some opting for TOE if no evidence of PFO exists on TTE where a high index of suspicion remains, and some only performing TOE to look at anatomy once a TTE has confirmed a PFO.[7] A PFO that is seen without Valsalva manoeuvre (indicating a permanent right to left shunt) is associated with a higher frequency of recurrent stroke and migraine.[8]

Method of closure

The association between PFOs and stroke, migraine and decompression illness, discussed in the next section, is remarkably consistent. To this end, there have been a number of studies looking at closure of PFOs to investigate whether this would alter clinical outcome. Surgical closure of a PFO for recurrent cryptogenic stroke occurred more commonly in the 1990s. However, percutaneous closure is now more commonplace. Percutaneous devices are implanted by placing a short sheath, into the femoral vein and then passing a wire up through the PFO to carry a trans-septal sheath, passing a device along this across the PFO into the left atrium, opening the left sided disc like an umbrella prior to pulling it against the inter-atrial septum and sealing it shut by

opening the right atrial disc. This is usually performed with simultaneous TOE or intra-cardiac echocardiographic imaging.

Device closure

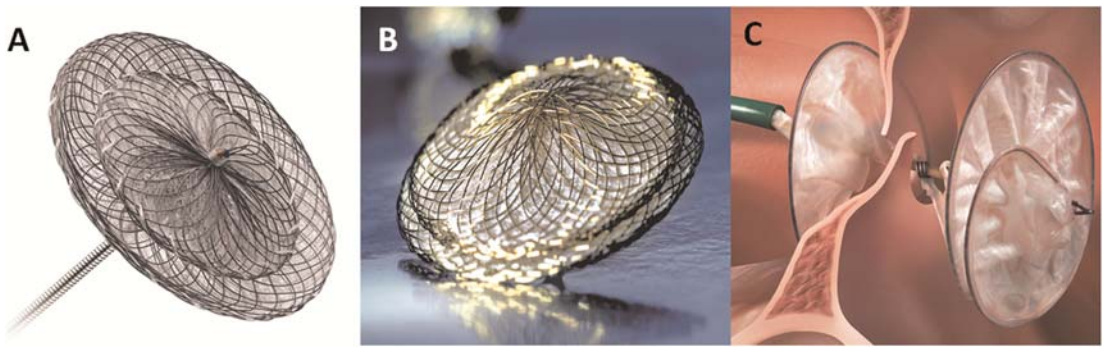
The varying designs allow the physician to tailor the device to the exact anatomy and size of the PFO (Figure 2). However, the common double umbrella design will fit most PFOs. Comparisons between devices have not generally been performed, and indeed a trial of this nature would be difficult to design, with possible endpoints, such as time to complete closure and periprocedural complications, being dependant on the operator as well as the device.

A prospective study in Germany that followed patients for a median of 24 months reported on periprocedural safety and follow-up in patients with three different PFO closure devices.[9] A total of 307 patients with cryptogenic stroke and a PFO with a mean age of 43 years underwent PFO closure using the PFO-Star ($n = 177$), Amplatzer Septal Occluder ($n = 69$) and Cardioseal/Starflex ($n = 61$). Choice of device was clinician dependent. The annual recurrence rate was 0.8% for endpoints of transient ischaemic attack (TIA), stroke and peripheral emboli, 0.8% with PFO-star; 0.7% with Amplatzer; and 1% with cardioseal/Starlex (compared with 3.4% in other observational registries).[10] After six months there was 69% closure and at two years 96% closure with no major differences in the rates of residual shunt between devices. Two patients required surgical device removal due to misalignment and device adherent thrombus. This study was unfortunately non-randomized, and as the type of device used was based on operator preference and experience, does not serve to provide an adequate comparison between devices. The periprocedural complication rate of 3% does, however, appear to be acceptable.

Given the recent concern about medical devices,[11] new devices need to be introduced with caution. Indeed, several previous devices have been withdrawn due to safety concerns or commercial reasons.[12]

Complication rates are low (<3% procedural) but can include stroke, heart attack, tamponade and device embolization.[9] The risk of arrhythmias is also low and may be reduced by PFO closure.[13] Devices may also need to be explanted for various reasons. A large retrospective study looked at data from a total of 13,736 patients in 18 institutions in whom occluder devices had been implanted with varying indications.[14] They found that 0.28% of devices were surgically explanted, the most common reason being chest pain presumed secondary to nickel allergy ($n = 14$). Other reasons stated included perforation of the atrium or aorta ($n = 2$), thrombus on the device ($n = 4$) and recurrent strokes ($n = 1$).

Figure 2
Selection of PFO closure devices in current use. (A) Amplatzer occluder (Amplatzer and St. Jude Medical are registered and unregistered trademarks of St. Jude Medical, Inc. Reprinted with permission of St. Jude Medical © 2012 all rights reserved.); (B) flex figulla occluder (image reproduced courtesy of Occlutech); (C) illustration of Gore Helex occluder *in situ* (image reproduced courtesy of Gore and Associates)



Surgical closure

Surgical closure of PFO is no longer commonplace, but underwent a series of small early studies looking for efficacy in prevention of recurrent paradoxical emboli. Ruchat *et al*. looked at 32 patients under 60 years old with cryptogenic stroke and PFO plus additional risk factors.[15] Two patients had residual shunting on TOE, but remarkably, no perioperative complications were seen and all patients who underwent the procedure had no recurrent vascular events or lesions on magnetic resonance imaging (MRI) over an average of 18 months of follow-up. Dearani *et al*. studied 91 patients with one or more strokes/TIAs presumed due to paradoxical emboli.[16] Morbidity included transient atrial fibrillation in 11, pericardial drainage for effusion in four, exploration for bleeding in three and superficial wound infection in one. Over a mean follow-up of two years no one had a stroke and eight had TIAs despite intact PFO closures proved on TOE. Unfavourable results such as this discourage isolated surgical closure of PFOs.[17] A trend for closure of PFOs found incidentally during surgery subsequently arose. A retrospective study on 13,092 patients operated on at the Cleveland Clinic in Ohio showed PFOs in 2277 using intraoperative TOE.[18] Out of these, surgical closure was performed in 28% and was more likely to be performed in younger patients (61.1 versus 64.4 years) and those with a prior history of stroke or TIA (16% versus 10%). Patients with repaired PFOs had an odds ratio of 2.47 of having a perioperative stroke compared with those with unrepaired PFO (17 versus 7 of 603 propensity matched patients; $P = 0.04$) and longer-term analysis showed no survival benefit from PFO closure.[18] The results must be interpreted in the light of it being a retrospective analysis, but perhaps serves to highlight the need for clear indications of PFO closure prior to undertaking it surgically; it may do more harm than good.

Radiofrequency ablation

Data does exist on PFO closure without the use of a device, instead using radiofrequency energy. This potentially removes a number of the procedural complications. However, the closure rate of 63% despite occasional need for a second procedure requires improvement.[19] This area is under active review.[20]

Indications for PFO closure

Stroke

Registries

An association exists between cryptogenic (unknown cause despite complete investigation) ischaemic stroke and PFO, with the theory that venous emboli pass paradoxically from the right-sided circulation to the left. This mechanism has been demonstrated in case images of thrombi stuck within PFOs.[21,22] A PFO is more commonly sought, and indeed more likely to be closed, in younger patients where there are few or no existing co-morbidities that predispose to stroke. The association was described by Biller *et al*. over 25 years ago.[23,24] A meta-analysis was performed in 2000 looking at a number of small observational studies with the inherent limitations of methodological differences and wide confidence intervals (CIs).[25] The odds ratio was 6 (95% CI, 3.72–9.68) for PFO in patients age <55 with cryptogenic stroke versus patients <55 with a known cause of stroke. Looking at patients <55 with cryptogenic stroke versus control subjects for presence of PFO, the analysis found an odds ratio of 3.10 (95% CI, 2.29–4.21) and for PFO plus atrial septum aneurysm (ASA) 15.59 (95% CI, 2.83–85.87).[25] This was confirmed in an analysis of studies in young patients by Homma *et al*.[26] A further random effects meta-analysis took into account the prevalence of PFOs found incidentally and compared patients with PFOs and crypogenic stroke to patients with stroke of known cause.[27] They found an odds ratio of 5.1 (95% CI, 3.3–7.8) in patients <55 years old with cryptogenic stroke versus patients with a known cause of stroke. The probability of the PFO being *incidental* to a cryptogenic stroke in patients <55 years old was only 20%, and 48% in older patients.[27]

A meta-analysis of 15 studies performed in 2009 looked at the recurrence rates of stroke in those with PFO versus in those without PFO in people who received medical treatment (antiplatelets or anticoagulants) and found no difference in recurrence in those with PFO.[28] This was despite the final pooled relative risks of recurrent events and recurrent stroke of 4.85 (95% CI, 3.43–6.27)

and 2.05 (95% CI, 1.39–2.71) respectively in the presence of a PFO.[29] Kent *et al.*, however, suggested a significantly lower prevalence of conventional risk factors in those with cryptogenic stroke and PFO versus without PFO, implying that a PFO generates a comparable risk that is not specifically treated by conventional medical therapy.[30] The same group published their own meta-analysis of observational studies and some smaller randomized trials (total 66 studies, 8916 patients but excluding results from the recently published CLOSURE trial), with a PFO undergoing closure versus medical treatment.[31] Again with the inherent limitations of such a meta-analysis they found a summary incidence ratio of 0.36 events (95% CI, 0.24–0.56) per 100 person years for those with closure versus 2.53 events (95% CI, 1.91–3.35) per 100 person years without closure.[31]

Trials

The CLOSURE trial of 909 patients with cryptogenic stroke/TIA and PFO split patients into treatment with PFO closure (447) or medical therapy (462) for a follow-up period of two years.[32] The cumulative incidence of death from any cause in the first 30 days after device implantation, or stroke/TIA/death from a neurological cause was 5.5% in the closure group and 6.8% in the medical therapy group (hazard ratio, 0.78; 95% CI, 0.45–1.37; P = NS). Although the study was not powered to look at the individual occurrences, there were no significant differences in these either. The control arm event rate is higher than the registries above, despite the fact that in most trials, patients tend to have better outcomes than in registries and more stringent follow-up, potentially biasing observational data.[33] There was also a significant occurrence of atrial fibrillation in the closure arm and a significant non-closure rate with the *Starflex* device used. This device is no longer commercially available, and device choice may have affected trial outcome.

The RESPECT trial was presented at TCT (Transcatheter Therapeutics, Miami, FL, USA) in October 2012. This was a trial of 980 patients randomized to PFO closure with an Amplatzer device.[35] Mean age was 46 years, and each patient had experienced a stroke (not TIA) within 270 days of randomization. It took eight years to recruit but was a very well conducted study. Safety was confirmed with 93.5% effective closure with the device (<10 bubbles on Valsalva). The primary endpoint was death from any cause within 45 days of randomization or ischaemic stroke (fatal or non-fatal). The primary endpoint was reached in nine patients in the closure arm and 16 in the medical arm (relative risk reduction, 46.6%; $P = 0.08$). However, there were three strokes in the device arm before closure had been performed. A pre-specified 'as treated' analysis (i.e. after closure) showed a relative risk reduction of 72% ($P = 0.0067$). Subgroup analysis suggested large shunts, and the presence of ASAs favoured closure. Large shunts were present in 75% of RESPECT compared with 50% in CLOSURE. The trial did not have as much follow-up in the medical arm as in the closure arm, and the protocol of medical therapy (aspirin alone in 46%, warfarin in 25%, Clopiodgrel alone in 14% and dual anti-platelet therapy in 14%) was perhaps not the current standard of care. However, the groups were well matched in all other ways. The event rate was lower than expected in the medical arm.

The PC trial was also presented at the same meeting. This was a trial of 414 patients with an average follow-up of four years. The trial included TIA, peripheral embolism and stroke. The average age was 54 years (10 years higher than RESPECT). This trial suggested a relative risk reduction with closure with an Amplatzer device of 37% ($P = 0.37$). The primary endpoint was death, stroke, TIA or peripheral embolism. It was interesting to note that the rate of atrial fibrillation was 2.5% in the closure arm and 1% in the medical arm, both much lower than in CLOSURE. This trial appeared underpowered compared with RESPECT.

Recommendations and conclusions

The result of the PC and RESPECT trials using the Amplatzer Occluder add to the debate about PFO closure. The RESPECT trial strongly suggests that in patients with cryptogenic ischaemic stroke proven on brain imaging, PFO closure appears safe and may well be effective in reducing recurrent events, especially in the presence of large shunts or an ASA. The data is not as clear for TIA. A meta-analysis of the data would be useful.[34,35]

National Institute for Health and Clinical Evidence (NICE) recommendations are in place from 2005, but new trial data is yet to be incorporated. Current guidance states that there are no major safety concerns with respect to the procedure of percutaneous PFO closure and that it can be considered an option in patients with cryptogenic stroke who have a PFO.[36] This is largely mirrored in the American Heart Association guidelines from 2006.[37]

Migraine

Registries

A retrospective study looked at the association between PFO and migraine while examining the link between PFO and decompression illness in 200 divers.[38] Migraine with aura (MwA) occurred more frequently in those with a large shunt versus those with a small shunt and those without a shunt (47.5% versus 10% versus 13.8%, respectively). A cross-sectional case control study with TOE on 93 patients with migraine and 93 patients without migraine showed that a PFO was present in 47% of patients with MwA compared with 17% of control subjects, giving an odds ratio of 4.56 (95% CI, 1.97–10.57), with a stronger association seen in those with larger shunts.[39] In 109 children with migraine, contrast TTE and TCD also demonstrated the PFO prevalence was significantly higher in those with MwA than in those with migraine alone (50% versus 35%; $P = 0.0004$), who had a rate of PFO presence similar to that of the general population ($P = 0.13$).[40] The aetiology behind the link remains unclear, although interestingly, the migraines were worse after dives, suggesting a mechanical hypothesis related to passage of bubbles to the brain.[38] A systematic review of studies performed in patients with migraine and PFO showed an odds ratio of 2.54 for the association, with clinical improvement seen post closure.[41]

Trials

The Migraine Intervention with Starflex Technology (MIST) trial recruited patients with moderate to large sized PFOs identified by contrast TTE who suffered from MwA, had frequent migraines and had failed two or more phases of prophylactic treatment.[42] A total of 147 patients were randomized to PFO closure with a STARFlex implant versus a sham procedure. The endpoint of cessation of migraines between 91 days and 180 days was reached in three out of 74 in the closure group versus three out of 75 in the sham group ($P = $ NS). The closure group suffered 10 serious peri-procedural events versus six in the sham group; four out of 10 may have been related to the device rather than to the procedure, and three patients had displacement/embolization of the deployed device that was then snared out. A total of five out of 74 patients randomized to the closure group were unable to have their PFOs crossed and residual moderate/large shunts were seen in four patients. The investigators did well to have an appropriate control group in the setup of the study; however, the complication rate was higher than in other studies and the results were disappointing. On exclusion of two patients considered to be outliers in terms of migraine burden, results did show a statistically significant effect. The follow-up period of 91 to 180 days for complete cessation of migraines is a stringent one and possibly contributed to the results of this study. Longer follow-up may be necessary for complete closure of the PFO. Reduction in migraine rather than 'cure' may have been more realistic a target.

A smaller study with longer follow-up looked at change of symptoms in patients with migraines refractory to medical treatment and PFO identified by TOE and TCD.[8] A total of 86 patients were divided into intervention or medical therapy prospectively based on physician assessment. As a result there was a bias with more patients having MwA, more severe migraine, greater degree of right to left shunt, specific pattern on TCD, coexisting inter-atrial septum aneurysm and clotting deficiencies in the group that received intervention. The Amplatzer occluder and the Premere closure devices were used. The results are clearly not randomized or controlled, but the complete lack of complications and the improvement in symptoms in all patients treated with intervention ($n = 40$) by the 29-month follow-up was impressive. Patients who had aura (32/40) all found that this had resolved at follow-up. The approach of being a more selective, tailored treatment, rather than blind randomization may have contributed to the positive results of this study. The ideal would be to have a sufficient number

of this type of hand-picked patient and then randomize them. This has proved difficult and some trials have been abandoned due to poor patient recruitment (MIST II).[43]

Conclusions and recommendations

The PRIMA and PREMIUM trials in migraine will certainly provide more data in this field.[44] Current NICE guidance states that PFO closure in migraine is not recommended outside of a trial.[45] The US Food and Drug Administration (FDA) has not approved any device to close PFOs, possibly due to limited evidence of one device over another but also the lack of clinical trial evidence of benefit.

Decompression

Registries

Decompression illness is found in divers and pilots flying at high altitudes. On ascent from high pressures (e.g. seabed) nitrogen that is normally found in tissue forms nitrogen bubbles that accumulate in the venous system. This is then filtered out by the pulmonary circulation if ascent is slow. In rapid ascent, the nitrogen bubbles forming directly in the arterial circulation can lead to wide ranging tissue trauma or vessel occlusion, causing a variety of symptoms from localized joint pain to paralysis. A PFO allows nitrogen bubbles to bypass the pulmonary 'filter' by short-cutting across the atria, thus allowing nitrogen bubbles to easily enter the systemic circulation.

Similar to cryptogenic stroke, a causative role has not been proven, but an association has again been shown between decompression illness and a PFO.[46] Historically, in asymptomatic divers, brain MRI scanning in some studies suggested increased white matter lesions in association with right-to-left shunting.[47,48] This has not been confirmed in all studies, however.[49,50] One study showed 29% of divers with a PFO suffering major decompression illness versus 6% without ($P = 0.016$), with a further association between the size of PFO and decompression illness lasting longer than 24 hours.[46] A further study identified large to medium PFOs present in 52% of affected divers versus 12.2% of unaffected historical control divers ($P < 0.001$).[38]

Trials

A recent trial reported on major neurological decompression events and ischaemic lesions on brain MRIs in divers with no PFO, with PFO choosing percutaneous closure and with PFO choosing conservative management for a follow-up period of five years (encompassing 18,394 dives).[51] They found no major neurological decompression events in the 'no PFO' group, 0.5 ± 2.5 major neurological decompression events per 10,000 dives in the PFO closure group and 35.8 ± 102.5 per 10,000 dives in the PFO non-closure group ($P = 0.045$) and with similarly significant results when looking at ischaemic lesions on brain MRI. This is highly suggestive that PFO is relevant in decompression illness.

Conclusions and recommendations

Based on the evidence up to 2010, which excludes the last study, NICE were cautious on the percutaneous closure of PFO in divers with recurrent paradoxical embolism, stating the possibility of serious procedural complications and recommend alternatives such as modification of diving practice. This may be altered once the results of the study by Billinger *et al*. are taken into account. As it stands, PFO closure in decompression is acceptable with appropriate patient counselling.[52] Stopping this recreational sport is the alternative, but this option is rarely accepted by dedicated scuba divers.

Conclusion

In experienced institutions where complications from PFO closure are low and clinical governance and audit procedures are in place, percutaneous PFO closure remains an option in younger patients with cryptogenic stroke, especially where medical therapy has failed or is contraindicated. The evidence presented does not come down firmly in one camp, suggesting that procedural risk must be offset against the risks of further embolic stroke. Consensus should be reached between the neurologist, cardiologist, and the patient. Anecdotal reports and some trial data of significant benefit in patients with migraines also warrant attention, but this is not clinically recommended currently. Recent data from divers

suffering from decompression illness suggest that in this group, PFO closure may well be warranted.

References

1 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

2 Cheng TO. The proper conduct of Valsalva maneuver in the detection of patent foramen ovale. *J Am Coll Cardiol* 2005;**45**:1145–6

3 Zanette EM, Mancini G, De CS, Solaro M, Cartoni D, Chiarotti F. Patent foramen ovale and transcranial Doppler. Comparison of different procedures. *Stroke* 1996;**27**:2251–5

4 Stendel R, Gramm HJ, Schroder K, Lober C, Brock M. Transcranial Doppler ultrasonography as a screening technique for detection of a patent foramen ovale before surgery in the sitting position. *Anesthesiology* 2000;**93**:971–5

5 Johansson MC, Helgason H, Dellborg M, Eriksson P. Sensitivity for detection of patent foramen ovale increased with increasing number of contrast injections: a descriptive study with contrast transesophageal echocardiography. *J Am Soc Echocardiogr* 2008;**21**:419–24

6 Monte I, Grasso S, Licciardi S, Badano LP. Head-to-head comparison of real-time three-dimensional transthoracic echocardiography with transthoracic and transesophageal two-dimensional contrast echocardiography for the detection of patent foramen ovale. *Eur J Echocardiogr* 2010;**11**:245–9

7 Kenny D, Turner M, Martin R. PFO closure in children. *Catheter Cardiovasc Interv* 2008;**71**:715

8 Rigatelli G, Dell'Avvocata F, Cardaioli P, *et al.* Permanent right-to-left shunt is the key factor in managing patent foramen ovale. *J Am Coll Cardiol* 2011;**58**:2257–61

9 Braun M, Gliech V, Boscheri A, *et al.* Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism. Periprocedural safety and mid-term follow-up results of three different device occluder systems. *Eur Heart J* 2004;**25**:424–30

10 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**:1083–8

11 MHRA. Medical Device Alert MDA/2012/008. 2012

12 Billinger K, Ostermayer SH, Carminati M, *et al.* HELEX Septal Occluder for transcatheter closure of patent foramen ovale: multicentre experience. *EuroIntervention* 2006;**1**:465–71

13 Jarral OA, Saso S, Vecht JA, *et al.* Does patent foramen ovale closure have an anti-arrhythmic effect? A meta-analysis. *Int J Cardiol* 2011;**153**:4–9

14 Verma SK, Tobis JM. Explantation of patent foramen ovale closure devices: a multicenter survey. *JACC Cardiovasc Interv* 2011;**4**:579–85

15 Ruchat P, Bogousslavsky J, Hurni M, Fischer AP, Jeanrenaud X, von Segesser LK. Systematic surgical closure of patent foramen ovale in selected patients with cerebrovascular events due to paradoxical embolism. Early results of a preliminary study. *Eur J Cardiothorac Surg* 1997;**11**:824–7

16 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**(19 Suppl):II171–II175

17 Gasiavelis N, Grinnemo KH, Lindblom D, Dellgren G. Surgical closure of patent foramen ovale in patients with suspected paradoxical embolism: long-term results. *Scand Cardiovasc J* 2004;**38**:375–9

18 Krasuski RA, Hart SA, Allen D, *et al.* Prevalence and repair of intraoperatively diagnosed patent foramen ovale and association with perioperative outcomes and long-term survival. *JAMA* 2009;**302**:290–7

19 Sievert H, Fischer E, Heinisch C, Majunke N, Roemer A, Wunderlich N. Transcatheter closure of patent foramen ovale without an implant: initial clinical experience. *Circulation* 2007;**116**:1701–6

20 Sohaib SMA UBK-KKM-LLKPMI. An evaluation of patent foramen ovale closure using radiofrequency ablation delivered with a robotic arm. *Journal of Heart Disease* 2011;**8**:321

21 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

22 Koullias GJ, Elefteriades JA, Wu I, Jovin I, Jadbabaie F, McNamara R. Images in cardiovascular medicine. Massive paradoxical embolism: caught in the act. *Circulation* 2004;**109**:3056–7

23 Biller J, Adams HP Jr., Johnson MR, Kerber RE, Toffol GJ. Paradoxical cerebral embolism: eight cases. *Neurology* 1986;**36**:1356–60

24 Biller J, Johnson MR, Adams HP Jr., Kerber RE, Toffol GJ, Butler MJ. Echocardiographic evaluation of young adults with nonhemorrhagic cerebral infarction. *Stroke* 1986;**17**:608–12

25 Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000;**55**:1172–9

26 Homma S, Sacco RL. Patent foramen ovale and stroke. *Circulation* 2005;**112**:1063–72

27 Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? *Stroke* 2009;**40**:2349–55

28 Almekhlafi MA, Wilton SB, Rabi DM, Ghali WA, Lorenzetti DL, Hill MD. Recurrent cerebral ischemia in medically treated patent foramen ovale: a meta-analysis. *Neurology* 2009;**73**:89–97

29 Kent D, Kitsios G, Hill MD, Almekhlafi MA, Wilton SB, Ghali WA. Recurrent cerebral ischemia in medically treated patent foramen ovale: a meta-analysis. *Neurology* 2011;**77**:301–2

30 Kent DM, Thaler DE. Is patent foramen ovale a modifiable risk factor for stroke recurrence? *Stroke* 2010;**41**(10 Suppl): S26–S30

31 Kitsios GD, Dahabreh IJ, Abu Dabrh AM, Thaler DE, Kent DM. Patent foramen ovale closure and medical treatments for secondary stroke prevention: a systematic review of observational and randomized evidence. *Stroke* 2012;**43**:422–31

32 Furlan AJ, Reisman M, Massaro J, *et al.* Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 2012;**366**:991–9

33 Kent DM, Kitsios GD. Percutaneous closure of patent foramen ovale: a near-perfect treatment ruined by careful study? *Circ Cardiovasc Qual Outcomes* 2012;**5**:414–5

34 Khattab AA, Windecker S, Juni P, *et al.* Randomized clinical trial comparing percutaneous closure of patent foramen ovale (PFO) using the Amplatzer PFO Occluder with medical treatment in patients with cryptogenic embolism (PC-Trial): rationale and design. *Trials* 2011;**12**:56

35 Carroll SD, Saver JL, Thaler DE, *et al.* Randomised evaluation of recurrent stroke comparing PFO closure to established current standard of care treatment. RESPECT Clinical Trial. See http://www.sjm.com/respect-data.aspx (last checked 5 November 2012)

36 NICE. Percutaneous closure of patent foramen ovale for the prevention of cerebral embolic stroke. 2005

37 Goldstein LB, Adams R, Alberts MJ, *et al.* Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2006;**113**:e873–e923

38 Wilmshurst PT, Pearson MJ, Walsh KP, Morrison WL, Bryson P. Relationship between right-to-left shunts and cutaneous decompression illness. *Clin Sci (Lond)* 2001;**100**:539–42

39 Schwerzmann M, Nedeltchev K, Lagger F, *et al.* Prevalence and size of directly detected patent foramen ovale in migraine with aura. *Neurology* 2005; **65**:1415–8

40 McCandless RT, Arrington CB, Nielsen DC, Bale JF Jr., Minich LL. Patent foramen ovale in children with migraine headaches. *J Pediatr* 2011;**159**:243–7

41 Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. *Cephalalgia* 2008;**28**:531–40

42 Dowson A, Mullen MJ, Peatfield R, *et al.* Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. *Circulation* 2008;**117**:1397–404

43 Clinicaltrials.gov. MIST II Trial. 2008

44 Tepper SJ, Cleves C, Taylor FR. Patent foramen ovale and migraine: association, causation, and implications of clinical trials. *Curr Pain Headache Rep* 2009;**13**:221–6

45 NICE. Percutaneous closure of patent foramen ovale for recurrent migraine. 2010

46 Torti SR, Billinger M, Schwerzmann M, *et al.* Risk of decompression illness among 230 divers in relation to the presence and size of patent foramen ovale. *Eur Heart J* 2004;**25**:1014–20

47 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**:701–5

48 Gempp E, Sbardella F, Stephant E, *et al.* Brain MRI signal abnormalities and right-to-left shunting in asymptomatic military divers. *Aviat Space Environ Med* 2010;**81**:1008–12

49 Koch AE, Kampen J, Tetzlaff K, *et al.* Incidence of abnormal cerebral findings in the MRI of clinically healthy divers: role of a patent foramen ovale. *Undersea Hyperb Med* 2004;**31**:261–8

50 Koch AE, Kirsch H, Reuter M, Warninghoff V, Rieckert H, Deuschl G. Prevalence of patent foramen ovale (PFO) and MRI-lesions in mild neurological decompression sickness (type B-DCS/AGE). *Undersea Hyperb Med* 2008; **35**:197–205

51 Billinger M, Zbinden R, Mordasini R, *et al.* Patent foramen ovale closure in recreational divers: effect on decompression illness and ischaemic brain lesions during long-term follow-up. *Heart* 2011;**97**:1932–7

52 NICE. Percutaneous closure of patent foramen ovale for the secondary prevention of recurrent paradoxical embolism in divers. 2010