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CORE TRAINING FOR DOCTORS

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Diagnosis and management of patent foramen ovale

A patent foramen ovale is a risk factor for cryptogenic stroke and migraine (Ghosh et al, 2007) with closure recommended by the National Institute for Health and Care Excellence (2013) to prevent recurrent thromboembolic events. This article examines the investigation and management of patent foramen ovale in current practice.

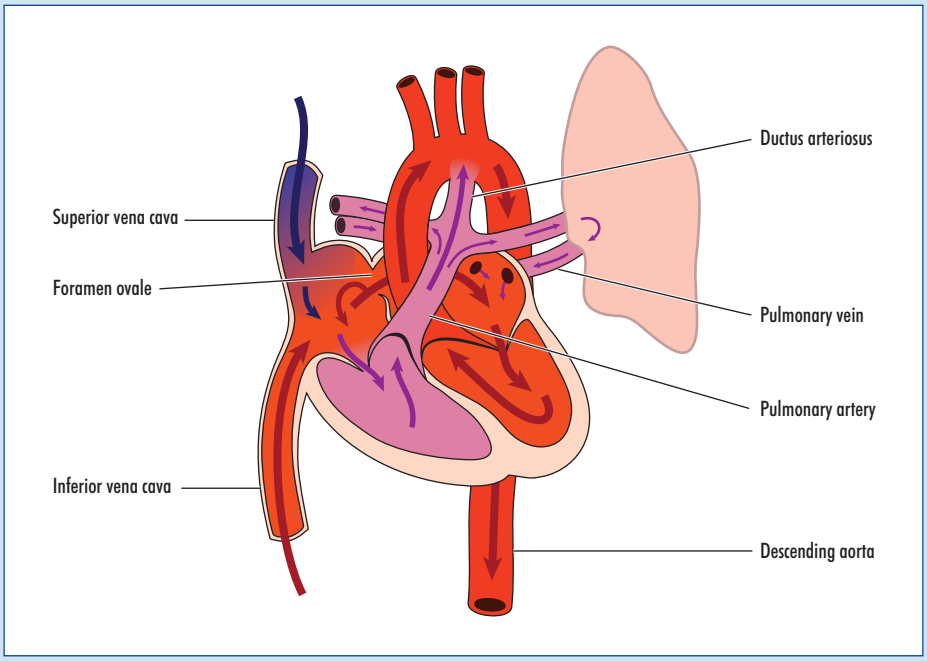
What is a patent foramen ovale?

The fossa ovalis is an overlap flap between the two layers of the atrial septum (septum primum on the left atrial side and septum secondum on the right atrial side). In the fetus there is communication between the left and right atria. Oxygenated blood drains from the umbilical vein via the ductus venosus to the inferior vena cava and then the right atrium. Blood does not flow to the fetal lungs as the pulmonary vascular resistance is high and instead goes via the foramen ovale and ductus arteriosus to the systemic circulation (*Figure 1*).

After the fetus is delivered, breathing causes the pulmonary vasculature resistance to fall with a subsequent increase in cardiac blood flow and increase in left atrial pressure. This causes the primum and secondum septae to fuse together, closing the foramen ovale. In 25–40% of individuals this closure is not complete and a flap or tunnel between the atria remains – the patent foramen ovale (Hagen et al, 1984) (*Figure 2*). In around 1% of the population, the septae are large and mobile and an atrial septal aneurysm exists (Silver and Dorsey, 1978).

The definition of an atrial septal aneurysm varies but a consensus view is that

Figure 1. Fetal circulation.



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the basal width of an atrial septal aneurysm should be more than 15 mm and the excursion of the aneurysm beyond the plane of the residual atrial septum should be at least 10 mm (Hanley et al, 1985). Atrial septal aneurysms are almost always associated with patent foramen ovale (Mattioli et al, 2001). The association of atrial septal aneurysm with cryptogenic stroke is debatable with some studies in favour (Handke et al, 2007) and some against (Di Tullio et al, 2007).

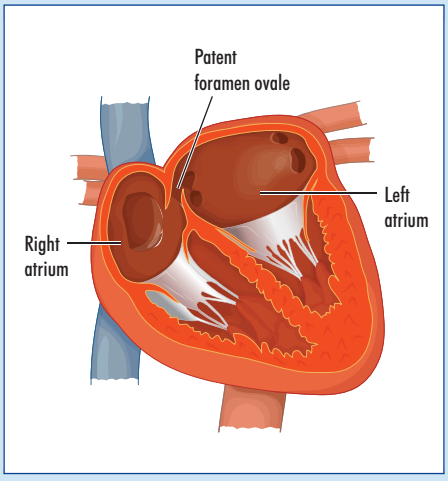
Presentation

Most patients with patent foramen ovale are asymptomatic. Some present with cryptogenic stroke or transient ischaemic attack. The underlying pathogenesis is not identified in up to 40% of cases of ischaemic stoke – the so-called cryptogenic stroke (Leys et al, 2002). Patent foramen ovale was first implicated in cryptogenic stroke in 1988 (Lechat et al, 1988). This association was then described in subsequent studies (Lamy et al, 2002) and in a meta-analysis (Overell et al, 2000).

Other rarer forms of presentation include migraine-like symptoms or decompression sickness (in divers) (Bonati et al, 2010). Rarer manifestations can include myocardial infarction (Agostoni et al, 2004), renal infarction (Carey et al, 1999) and fat embolism (Pell et al, 1993).

The theoretical mechanism behind presentation is 'paradoxical embolism' in which a clot goes across the patent foramen ovale from the right atrium to the left atrium and thence to the systemic circulation (Kutty et al, 2012).

Figure 2. Anatomy of the patent foramen ovale.



Diagnosis

When a patent foramen ovale is suspected first-line diagnostic investigations are imaging, including transthoracic echocardiography, transoesophageal echocardiography or transcranial Doppler. A patent foramen ovale can occasionally be identified as an incidental finding.

Transthoracic echocardiography

Transthoracic echocardiography is often the first-line investigation as it is widely available, cheap and can rule out other potential cardiac sources of stroke (Maffè et al, 2010). However, while colour flow may be seen across the atrial septum, this is not visualized in the majority of cases of patent foramen ovale.

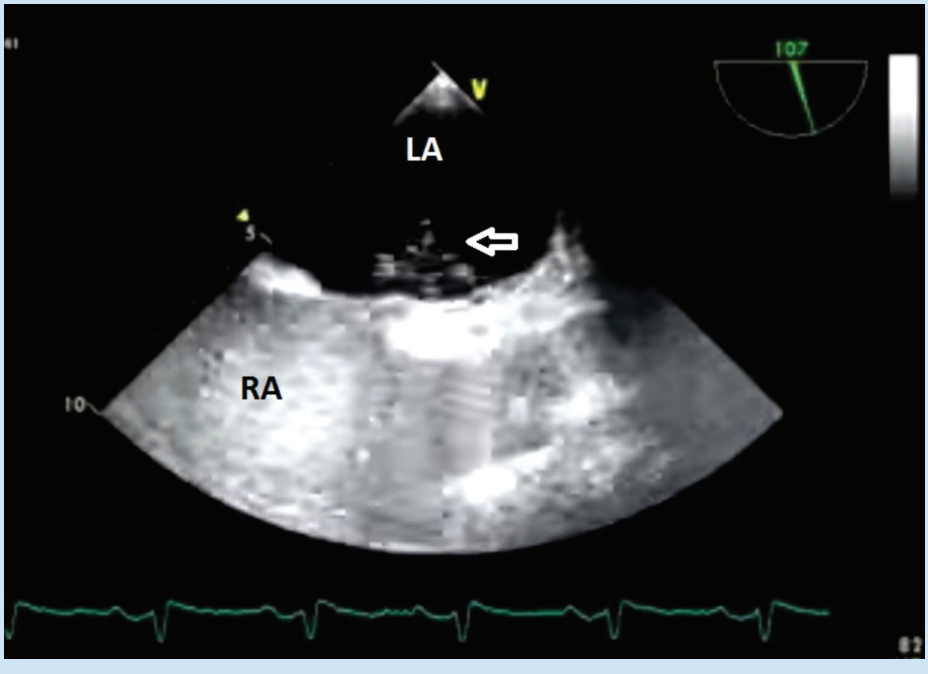
Agitated saline contrast is routinely used to better interrogate the atrial septum. This is injected during a Valsalva manoeuvre and the patient is asked to release strain when contrast is seen in the right atrium. The Valsalva manoeuvre increases intrathoracic pressure and reduces venous return. This causes a decrease in pulmonary blood flow and left atrial pressure, allowing blood to flow from the right atrium to the left atrium if there is a hole in between (Zanette et al, 1996). If contrast microbubbles are seen passing from the right atrium to the left atrium across the atrial septum during release, a patent foramen ovale is present (*Figure 3*).

The timing of the appearance of the microbubbles is important. If microbubbles are seen in the left atrium before they appear in the right atrium or are seen in the left atrium more than five heart beats after they appear in the right atrium, an anomalous venous connection to the left atrium or a pulmonary arteriovenous malformation may be present. Ideally, contrast should be injected through the femoral vein. This is to prevent wash away by contrast-free blood directed from the inferior vena cava via the Eustachian valve which may occur if injected via an upper extremity vein, resulting in a false-negative result (Gin et al, 1993; Schuchlenz et al, 2006). However, this is not always practicable in the outpatient setting. It should also be noted that if microbubbles are seen freely crossing the patent foramen ovale without the requirement of a Valsalva manoeuvre, there is a greater likelihood of recurrent stroke and migraine-like symptoms (Rigatelli et al, 2011).

Transoesophageal echocardiography

Transoesophageal echocardiography is superior to transthoracic echocardiography in the detection of patent foramen ovale

Figure 3. Transoesophageal echocardiogram still image demonstrating microbubbles (arrow) crossing from right atrium (RA) to left atrium (LA) across a patent foramen ovale. Agitated saline contrast is seen opacifying the right atrium.



(DeRook et al, 1992). The atrial septum is closer to the probe in transoesophageal echocardiography which allows better direct visualization of the septum and is especially useful in determining if a percutaneous approach to closure is feasible or not. Transoesophageal echocardiography may be a routine second-line investigation in some centres, depending upon availability (Kenny et al, 2008), while in other centres it may be carried out if a strong clinical suspicion of patent foramen ovale remains despite a normal contrast-transthoracic echocardiography study. However, transoesophageal echocardiography is more invasive than transthoracic echocardiography and performing the Valsalva manoeuvre may be difficult.

Transcranial Doppler

Transcranial Doppler may be the first-line investigation, especially in neurological units. After the peripheral injection of agitated saline contrast, blood flow in the middle cerebral artery is imaged before and after a Valsalva manoeuvre. Transcranial Doppler has a greater sensitivity for detecting patent foramen ovale than transoesophageal echocardiography, but it has poorer specificity as it cannot reliably distinguish between patent foramen ovale and arteriovenous malformations (Stendel et al, 2000).

Management

The optimal treatment for patent foramen ovale in those with a thromboembolic event remains equivocal, with medical options including anticoagulation (warfarin) or antiplatelet therapy (aspirin). In some cases closure (either percutaneous or surgical) may be deemed appropriate to prevent recurrence. This is recognized in the National Institute for Health and Care Excellence (2013) guidance. Prophylactic closure is not recommended in cases where patent foramen ovale is an incidental finding (Meissner et al, 2006).

Medical management

Aspirin and warfarin are commonly used to prevent recurrent thromboembolic events in those with a patent foramen ovale. The evidence favouring one over the other is inconclusive, with the PFO in Cryptogenic Stroke Study showing that there was no difference in delaying recurrent ischaemic stroke or death in patients randomized to aspirin or warfarin (Homma et al, 2002). In addition, numerous studies have shown high rates of recurrent ischaemic cerebrovascular events with medical management (Mohr et al, 2001; Khairy et al, 2003; O'Gara et al, 2009).

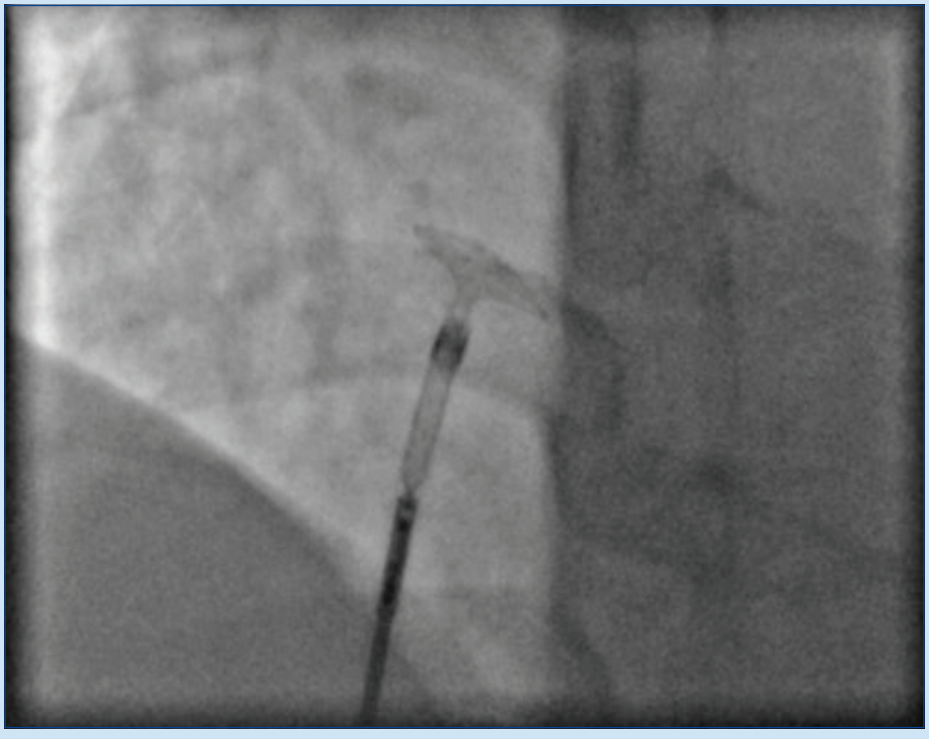
Percutaneous therapy

Transcatheter closure under fluoroscopic guidance was first described by Bridges and colleagues in 1992. Since then the field has evolved dramatically with improvements in patient selection and device availability driving the expansion. A number of trials have demonstrated the safety of this approach (Mas et al, 2001; Braun et al, 2004) although there have been issues with some devices (Billinger et al, 2006). Currently, commonly used devices include the Amplatzer occluder (St. Jude Medical Inc.) (*Figure 4*), Flex Figulla occluder (Occulutech) and Gore Helex occluder (Gore and Associates). Trials between devices have not been performed and choice of device is based on operator preference and experience. Devices are inserted via the femoral vein over a wire. Under fluoroscopic guidance, the umbrella-like left atrial part of the device is manoeuvred across the patent foramen ovale, opened and then pulled back against the atrial septum. The right atrial part of the occluder is then opened against the atrial septum to seal the patent foramen ovale (*Figure 5*).

Transoesophageal echocardiography is routinely used both pre-procedurally to determine suitability of a percutaneous closure strategy and peri-procedurally to ensure optimal positioning of the occluder. The risk of a serious complication is low (<5% in experienced centres) but may include tamponade, arrhythmias, stroke, myocardial infarction and embolization of the device (Braun et al, 2004).

Figure 4. Patent foramen ovale closure device. (Amplatzer occluder).

Figure 5. Fluoroscopic image of patent foramen ovale device in position (before deployment).



Surgical closure

Surgical closure of a patent foramen ovale may be attempted if the anatomy is unfavourable for percutaneous closure. The data in favour of surgical closure are limited and the long-term efficacy has been called into question with one series showing an annual combined stroke or transient ischaemic attack recurrence rate of nearly 8% post procedure (Dearani et al, 1999). This is in comparison to a reported recurrence rate of up to 5% with a percutaneous closure strategy (Sievert et al, 2001; Wahl et al, 2001; Kutty et al, 2008).

Controversy: patent foramen ovale and migraine

A relationship between migraine with aura and patent foramen ovale was first postulated in the 1990s (Del Sette et al, 1998). It was also shown that divers with decompression illness and right to left shunts had a higher prevalence of migraine with aura compared to divers with a small shunt or no shunt (Wilmshurst et al, 2001). Thereafter some reported resolution of migraine and aura after shunt closure (Azarbal et al, 2005). However, no association was seen between patent foramen ovale and migraines in a case control study (Garg et al, 2010) and a randomized control trial evaluating the effect of patent foramen ovale closure on migraine with aura showed no significant decrease in migraine cessation with patent foramen ovale closure (Dowson et al, 2008).

Another disappointing recent trial was PRIMA (PFO Repair in Migraine With Aura) which was presented at Transcatheter Cardiovascular Therapeutics 2014. Participants with patent foramen ovale closure had a non-significant reduction in days with headache compared to those on medical therapy. Results from the ongoing PREMIUM (Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the Amplatzer PFO Occluder Compared to Medical Management) trial are awaited. Currently National Institute for Health and Care Excellence does not recommend patent foramen ovale closure for migraine in routine practice.

Controversy: recent trials

While there is controversy regarding best medical management of a patent foramen ovale (as previously described), there is also ongoing active debate regarding the percutaneous device closure approach.

CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale) was the first independent prospective randomized control trial investigating device occlusion of patent foramen ovale (Furlan et al, 2012). Device closure *vs* medical therapy was compared in adult patients with patent foramen ovale presenting with cryptogenic stroke or transient ischaemic attack. The primary composite end point was stroke or transient ischaemic attack during 2 years of follow up, death from any cause during the first 30 days, or death from neurological causes between 31 days and 2 years. There was no statistically significant difference in the cumulative incidence of the primary end point between the two groups. Major procedure-related vascular complications were seen in 3% of cases and 5.7% suffered periprocedural atrial fibrillation. The authors felt that their findings did not preclude a role for device closure but that rigorous patient selection was required.

Two further studies which investigated the role of device closure in patent foramen ovale – RESPECT (Randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care) (Carroll et al, 2013) and PC Trial (Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism) (Meier et al, 2013). Both concluded that percutaneous device closure failed to prevent subsequent stroke or other adverse effects. However, in the main intention-to-treat analysis in the RESPECT trial, there was a trend to lower rates of stroke recurrence with patent foramen ovale closure than with medical therapy, but this was not statistically significant. Again sub-analysis in this trial suggested that closure provided greater protection than medical therapy in patients with substantial (grade 3) right-to-left shunt across the patent foramen ovale (hazard ratio = 0.18, 95% confidence interval = 0.04–0.81) and atrial septal aneurysm (hazard ratio = 0.19, 95% confidence interval = 0.04–0.87). In PC Trial, over a mean follow-up duration of approximately 4 years, results for the primary end point (composite of death, non-fatal stroke, transient ischaemic attack or peripheral embolism) as well as the individual component end points of non-fatal stroke and transient ischaemic attack all favoured closure but did not reach statistical significance. The authors postulated that the lack of statistical significance may be the result of a type II error as the trial was underpowered.

The evidence definitively favouring closure remains elusive as reflected by a number of meta-analyses on the topic (Agarwal et al, 2012; Kwong et al, 2013; Rengifo-Moreno et al, 2013) and an editorial entitled 'Still no closure on the question of patent foramen ovale closure' (Messé and Kent, 2013).

Conclusions

Further trials are needed (and are ongoing) to determine best practice in managing patent foramen ovale and an exciting future lies ahead as technological advancements in the field grow. BJHM

KEY POINTS

- Patent foramen ovale is detected in more than half of young patients with cryptogenic stroke.
- Atrial septal aneurysm is more common in patients with patent foramen ovale and cryptogenic stroke.
- Echocardiography (transthoracic echocardiography or transoesophageal echocardiography) with agitated saline contrast injection is the most common baseline investigation for diagnosis and planning a percutaneous strategy (transoesophageal echocardiography). Transcranial Doppler may also be used for diagnosis.
- Evidence in favour of medical therapy is lacking.
- The National Institute for Health and Care Excellence has approved device closure therapy but data in favour of device closure are inconclusive.
- Surgical closure is a rarely used option.

Figure 4 *is reproduced courtesy of St Jude Medical Inc.*
Conflict of interest: none.

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