What General Practitioners need to know about Patent Foramen Ovale

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ABSTRACT

Background

A patent foramen ovale (PFO) consists of a hole between the right and left atriums of the heart that did not close the way it should after birth. Twenty five percent of the population have a PFO, but this usually does not cause problems, because the opening is functionally closed by the difference in pressure between the heart and the chest.

Method

This study is a literature review about the clinical significance of PFO and its management in three clinical situations: cryptogenic strokes, migraine with aura and scuba divers who sustained a decompression sickness.

Results and conclusion

PFOs had been linked with various medical conditions such as strokes, migraine, and with certain types of decompression sickness (DCS). In general, this association is not very well established. Young patients who sustain a cardiovascular event without a known cause (cryptogenic stroke) have resulted in the tendency to screen these patents becoming the norm and more PFOs are being closed using standard methods and devices. The association of PFOs and migraine attacks is less clear. In the case of scuba divers the risk of suffering from a decompression accident is increased if one has a PFO. The management of these patients remains difficult.

Keywords

Patent foramen ovale, cryptogenic strokes, migraine, decompression sickness

INTRODUCTION

A PFO is a defect in the septum between the two atrial chambers of the heart. Specifically, the defect is an incomplete closure of the atrial septum that results in the creation of a flap or a valve-like opening in the atrial septal wall. A PFO is present in everyone before birth but seals shut in about 75 to 80 per cent of the population. The cause of a PFO is unknown. There are no known risk factors. PFOs have been found on autopsy in up to 35 per cent of the healthy population (Laskowski, 2012).

PFOs AND CRYPTOGENIC STROKES

Crytogenic strokes are those cerebrovascular accidents in usually young patients where the cause remains unknown despite extensive diagnostic work up. This type of stroke amounts to forty percent of all strokes (Sacco, et al., 1989). The prevalence of a PFO is approximately doubled among cryptogenic stroke (CS) patients. Regardless of mechanism, nearly 30,000 young patients each year have a cryptogenic stroke and a PFO. This has generally been attributed to paradoxical embolism, and many physicians recommend PFO closure to prevent recurrence (Kent and Thaler, 2010). Since 1988, studies have shown that a PFO is significantly more frequent in young stroke patients (less than 55 yrs) than in matched control subjects, and paradoxical embolism has been suggested as the main mechanism of stroke in these patients (Rodriguez and Homma, 2003). Nonetheless, another study on 68 patients aged less than 55 years concluded that paradoxical embolism is not the primary mechanism of stroke in patients with a patent foramen ovale (Ranoux, 1993).

The association in older patients remains uncertain as only a few studies have included patients more than 55 years old. Nonetheless, one study confirmed the association between the presence of a PFO and CS in both patients younger than 55 years of age and those 55 years of age or older (Handke, 2007).

The question at present is whether we should screen patients for PFOs and what the managment should be when a PFO is discovered. Optimal management at present is still desirable. There are ongoing studies and trials to compare the effectiveness of percutaneous closure of the PFOs with medical therapy and to study the outcomes in the hope of issuing guidelines for the management of these patients. The Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment was an industry-sponsored trail (Respect Trial, 2012). This trial, started in 2007, recruited 900 participants aged between 18 and 60 years. The trial was concluded in August 2012. Patients who had a cryptogenic stroke within the last 270 days and patients who have been diagnosed with a PFO were included. Those found to have a PFO had an intervention to close the defect using a Amplatzer PFO Occluder device and later tested to ensure a successful procedure by using transthoracic echocardiography (TTE) and bubble studies. These patients were compared with patients who were treated medically using aspirin alone, Coumadin alone, Clopidogrel alone, or Aspirin combined with Dipyridamole. For carefully selected patients with history of cryptogenic stroke and PFO, the Respect Trial provided evidence of benefit in stroke risk reduction from closure with the Amplatzer PFO Occluder over medical management alone. Stroke risk reduction was observed across the totality of analyses with rates ranging from 46.6% - 72.7%. PFO closure with the Amplatzer PFO Occluder exposed patients to a very low risk of device- or procedure-related complications. RESPECT remains the best trial showing the benefits of PFO closure in reducing the incidence of associated stroke.

Another trail included the Evaluation of the STARFlex Septal Closure System in Patients with a Stroke or TIA due to the Possible Passage of Clot of Unknown Origin through a PFO (Closure 1). Preliminary results from this trial showed that alternative explanation unrelated to paradoxical embolism present in 80 per cent of patients with recurrent stroke or TIA and that percutaneous closure with STARFlex® plus medical therapy does not offer any significant benefit over medical therapy alone for the prevention of recurrent stroke or TIA in patients $\leq$ aged 60 presenting with cryptogenic stroke or TIA and a PFO. The other trial was the PC (Percutaneous Closure-Trial: PFO and Cryptogenic Embolism (Khattab, et al., 2011). However, patients taking part in these trials were all 60 years or younger on enrollment. Further trials with older participants are needed in order to develop diagnostic and therapeutic guidelines. Another trial which can throw some light on this, is the ongoing trial by Kent and Thaler (2011) called the Risk of Paradoxical Embolism (RoPE) Study which is aimed to develop and test a set of predictive models that can identify those patients most likely to benefit from preventive treatments for PFO-related stroke recurrence, such as PFO closure. The study is still ongoing. A study by Akhondi, et al., (2010) which evaluated the relationship between the morphological and functional size of the PFO showed that PFO size or morphology should not be used as the only criteria to decide whether a PFO should be closed.

PFOs AND MIGRAINE

An association between migraine with aura and PFO with shunting has been suggested (Tepper, Sheftfell & Bigal, 2007). An association of migraine with aura and Osler-Weber-Rendu disease has also been proposed, with the mechanism likely to be shunting though pulmonary arteriovenous malformations (Dalla Volta, et al., 2005). This study confirmed previous observations of a link between migraine with aura, cluster headaches and PFO. The study also suggested that such an association was independent to migraine clinical phenotype and was probably unrelated to the pathogenic mechanism of paradoxical embolism.

In a quantitative systematic review, a low to moderate level of evidence for the association between migraine (with or without aura) and PFO was found (Schwedt, Demaerschalk and Dodick, 2008).

Six studies of the effects of PFO closure on migraine showed an improvement but had a very low grade of evidence. The low-to-moderate grade of evidence from observational studies supported an apparent association between PFO and migraine. Although PFO closure seemed to affect migraine patterns favourably, the very low grade of available evidence to support this association precluded definitive conclusions. It has already been stated that prospective, controlled, clinical trials designed to evaluate the efficacy and safety of percutaneous device closure of PFO for migraine prevention were needed (Schwedt and Dodick, 2006).

On the other hand, in a multi-ethnic, elderly, population-based cohort, it was found that the presence of a PFO was not associated with self-reported migraine. This study also showed that the causal relationship between PFO and migraine remained uncertain, and

the role of PFO closure among unselected patients with migraine remains questionable (Rundle, et al., 2008). On the other hand, a case control study showed that compared with medical treatment, closure of PFO brings about a significant overall improvement in migraine. This seems to occur irrespective of migraine type and of previous cerebrovascular disease (Anzola, et al., 2006). In addition to the overall improvement in migraine with aura, the occurrence of aura is dramatically reduced. In a study of 121 patients with migraine it was again found that there is a possible association of migraine with aura and PFO. But it seems that PFO does not influence the type of aura and frequency of attacks of migraine as well as it is not associated with familial occurrence of migraine (Domitrz and Mieszkowski, 2008).

PFOs AND MYOCARDIAL INFARCTION

PFOs have been implicated as being also a risk factor not only for stroke and migraine but also for myocardial infarction and other ischemic vascular events (Diener, Tobias and Dodick, 2007). Although we have this evidence, explanation for these associations remains desirable.

PFOs AND SCUBA DIVERS

Right-to-left shunts are also associated with certain forms of neurological decompression sickness (DCS) in SCUBA (self-contained underwater breathing apparatus) divers (Wilmshurst and Bryson, 2000). The neurological decompression illness can occur after normal dives according to decompression tables, as a result of paradoxical gas embolism. A small number of observations suggested that cutaneous decompression illness was also associated with a right-to-left shunt, although embolic aetiology of a diffuse rash was more difficult to explain (Wilmshurst, et al., 2001). Cutaneous decompression illness has two possible mechanisms. The first mechanism was associated with a large right-to-left shunt, when it seemed that paradoxical gas embolism from peripheral bubble emboli invaded tissues supersaturated with nitrogen. Secondly, cutaneous decompression illness could occur in individuals without a shunt. In these subjects, the mechanism might be bubble emboli passing through an 'overloaded' lung filter or autochthonous bubble formation (Wilmshurst, et al., 2001). PFOs that caused DCS were 8mm in diameter or more (the larger the area the greater the shunting and the greater the chance of a DCS). PFOs which are smaller in diameter are found in about 15 per cent of the general population, but in only about 3 per cent of these did shunt related DCS occur. Also the diameter of a PFO is only partly correlated with propensity to shunt, because additional factors, such as mobility and stiffness of the flap covering the PFO, right atrial pressure that varies with activities, and atrial flow characteristics affect shunting (Wilmshurst, 2012). Today, we know that virtually most types of bends affecting the skin are related to right to left shunts across a PFO. We have more data about PFOs than many other fitness-to-dive issues, so if anyone has a cutaneous decompression illness, this is more likely to be PFO related, and therefore, the diver involved merits to be screened for a PFO (Wilmshurst, 2012).

The United Kingdom Sport Diving Medical Committee (UKSDMC) meeting about screening agreed that it was not reasonable to screen all, but that the potential groups where screening may be appropriate would be those with a previous DCS and those with migraine with aura (UKSDMC, 2001).

The rationale is that a diver who has a documented PFO, theoretically, has an increased risk of DCS. He has to make a more reasonable risk assessment if he wants to do high decompression stress diving. Having the test does not commit him to a closure procedure. He may simply modify his diving. If a diver had a history of migraine with aura, and suffered even once decompression illness, he should be definitely screened for a PFO. Current evidence on the efficacy of percutaneous closure of PFO for the secondary prevention of recurrent paradoxical embolism in divers is inadequate in quality and quantity, and the evidence on safety shows that there is a possibility of serious complications. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or reseach (NICE, 2010).

Screening tests for PFOs and the subsequent closure procedure can be a costly business, so the decision to go ahead is not a light one to take. The patients needing to know whether they have a PFO need to be counselled about why they want to know and what they will do with the information and disadvantages of knowing (such as adverse effects on insurance premiums). This strategy actually takes longer than it takes to close a PFO. So essentially, at present, the criteria for doing a contrast echo include divers with migraine with aura and no history of DCS and divers who are about to go to do some high risk diving in a

place remote from recompression facilities. Otherwise, the only candidates for screening for PFO are divers who have had a DCS and intend to persist with diving, young people who sustained some form of cryptogenic strokes and those patients awaiting posterior fossa neurosurgery Wilmshurst, 2012).

CONCLUSION

For carefully selected patients with history of cryptogenic stroke and PFO, the Respect Trial provides evidence of benefit in stroke risk reduction by closure with the Amplazter PFO Occluder over medical management alone. The PFO size or morphology should not be the only criteria to decide whether a PFO should be closed in case of paradoxical embolism. The link between PFOs and DCS has been amply demonstrated. The closure of the PFO, when it was done well, resulted in a reduction in the risk of a DCS. The occurrence of a PFO in divers who had a DCS may be of consequence and its closure may be contemplated. The association between migraine and PFOs is not well established. No sound evidence exits so far that closure of PFOs will reduce the incidence of migraine.

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