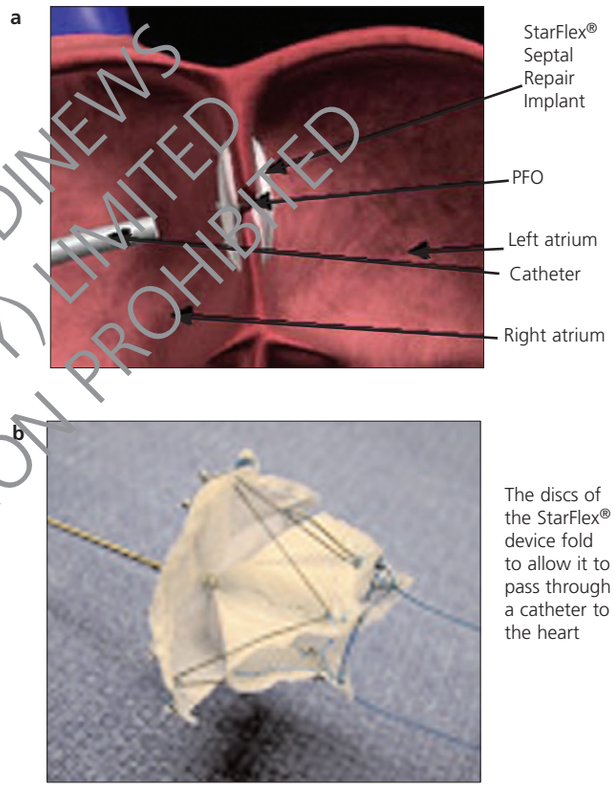
PFO: to close or not to close – a headache decision

Patent foramen ovale (PFO) is defined as a communication at the fossa ovalis between the primum and secundum atrial septa that persists after the first year of life. *In utero* the PFO functions as a physiological conduit for right to left shunting and it functionally closes at birth once the pulmonary circulation is established and there is a rise in left atrial pressure. This is followed by anatomical closure of the septum primum and septum secundum by one year of age.

It is estimated that up to 15% of the population have a PFO that can be demonstrated on transthoracic echocardiography and up to 27% of patients at autopsy have identifiable PFOs. This difference is because autopsy allows direct visualisation whereas echocardiography relies on measurements of an indirect physiological phenomenon.

Most patients with isolated PFOs are asymptomatic and have a normal clinical examination. The most recognised risk of this inter-atrial communication, however, is ischaemic stroke or transient ischaemic attack (TIA). PFOs are more commonly found in stroke sufferers under the age of 55 with no other identifiable cause compared to the normal population.[1] Large PFOs pose more risk of stroke than small ones.[2] Other associated risks are pulmonary emboli,[3] chronic obstructive disease,[4] decompression sickness or 'the bends',[5] and paradoxical emboli to other organs.[6] More recently, an association between PFOs and migraines has been hypothesised.

Figure 1. **a**: Percutaneous closure of patent foramen ovale (PFO) can now be achieved with devices such as the StarFlex® occluder; **b**: shows how the discs of the device fold to allow it through a catheter to the heart



Management

Treatment of PFOs includes medical management, percutaneous closure or surgical intervention. Antiplatelet therapy or formal anticoagulation are the mainstay of medical management and there is no clear difference in studies comparing the two therapies.[7]

Percutaneous closure is now possible following advances made in closing other atrial septal defects (ASDs). The Rashkind® occluder (also known as CardioSeal® and more recently as StarFlex®) was inserted in the 1980s (figure 1). A more recent device first implanted in 1997, the Amplatzer® PFO occluder, has the advantage of being self-centering. Both devices can be used under fluoroscopic and echocardiographic guidance. Antibiotic prophylaxis and antiplatelet therapy are recommended for three to six months post-procedure. Approximately 10% of patients report palpitations after implantation of the device. These often resolve spontaneously but some patients do suffer from paroxysmal or persistent atrial fibrillation. Other potential complications are infection, erosion into the pericardium or aorta at the rim of the device, creating a new ASD by tearing the thin septum primum, embolisation of the device during or after implantation and thrombosis.

Surgical closure is either primary through the use of sutures to close the opening, or secondary where a tissue patch is used. Disadvantages of this approach are the invasive nature of the operation and the usual risks of bypass cardiac surgery.

PFOs and migraine

There has been much debate recently on a possible link between PFOs and migraine. The hypothesis is that atrial communication allows tiny impurities, hormones or chemicals into the left side of the heart without being filtered by the lungs. These trigger migraines when they reach the brain. Migraines affect 10% of the population and are estimated to cost the economy approximately £750 million pounds a year in lost production. They are twice as common in women than men. Current treatment is based on prophylaxis to manage triggers and terminate attacks using both pharmacological and non-pharmacological methods.

Retrospective observational studies in 2003 through questionnaires completed by 69 post-stroke patients showed a benefit in migraine symptoms after PFO closure. Of the 50 who had suffered from migraines prior to their PFO closure, 82% reported an improvement.[8] Later the same year Windecker[9] illustrated a similar improvement in a survey of 215 young stroke victims after PFO closure. Patients reported an 80% reduction in frequency of attacks, with 25% being totally free of migraine attacks. In 2004 a similar questionnaire demonstrated benefits in patients both with and without auras post-PFO closure.[10] Reisman[11] in 2005 set out to quantify the benefits of PFO closure on frequency and severity of migraine and reported an 80% reduction in the average number of attacks per month in 162 stroke patients, with 56% experiencing a complete resolution of their symptoms.

The MIST trial (Migraine Intervention with STARFlex® Technology), a prospective, randomised, double-blind, placebo-controlled trial, is now evaluating the exact nature of the PFO-migraine link. Early results are promising. Enrolment was completed six months ahead of schedule when 14,000 migraine sufferers immediately volunteered for the trial after its announcement in January 2005. Transoesophageal echocardiography confirmed whether the PFO was suitable for closure and then patients were either randomised to PFO closure with the StarFlex® septal repair or a sham procedure control group. The patients, but not the physicians, were blinded to the randomised treatment. Patients were treated with aspirin and clopidogrel for three months and followed up for six months to see whether there was any improvement in the migraine frequency and severity.

Of the volunteers, 432 migraine sufferers with aura were found to have a PFO, of which 147 were enrolled into the study (84% were women, with a mean age of 44 years). Inclusion criteria were: one year documented medical history of migraines with aura, migraines with aura at least five times a month, free of headaches at least seven days a month, and no therapeutic effect with two classes of prophylactic medication. Patients were excluded from the trial if there was any cardiac contraindication, prior stroke or TIA, or migraine medication overuse.

Interestingly, among the 432 patients screened in the trial, 60.2% had an atrial right-to-left shunt, much higher than typically found in the general population. A large atrial shunt was present in 37.7% of patients, with a small shunt in 16.7% and no shunt in 39.8%. Prior population-based studies have shown PFOs are present in 27% of the general population, with 7% being large PFOs. The mean diameter of PFO in the trial was 9.21 mm.

The primary end point in MIST was absence of migraine during three months' follow-up after clopidogrel discontinuation. This was calculated on findings from previous observational studies. Preliminary analysis revealed no difference between the groups in the primary end point of absence of migraines: three patients in each group achieved this target. But in the PFO closure group the number of headache days was significantly reduced by 50% compared to the control group (42% *vs.* 23%; p=0.038). There was also a reduction in the headache burden, defined as the frequency multiplied by the duration of the headache, from 136.1 at baseline to 86.06 at follow-up in the PFO closure group (p=0.033) and from 116.8 at baseline to 96.32 at follow-up in the control group (p=NS).

Although PFO closure was not associated with a difference in the total migraine cessation compared with the sham procedure in this trial, the reductions in headache days and migraine burden are promising. The final results of MIST will be announced later in the year and a second trial, MIST II, is currently being conducted in the US to assess the benefits of PFO closure. A third trial, MIST III, is proposed as a planned extension to the original MIST I trial. This will give patients who received the sham procedure in the original study, the option to undergo percutaneous closure and will extend follow-up for all PFO closure patients for an additional 18 months. It is hoped that these results will help to determine which patients should be referred to interventional cardiologists for further treatment.

Conflict of interest

None declared.

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