

PFO Closure

Right-to-left shunts are associated with arterial hypoxaemia, cryptogenic ischaemic stroke, decompression illness, migraine with aura and transient global amnesia. The most frequently cause of a right-to-left shunt is a large persistent (or patent) foramen ovale (PFO). A non-causal association between these conditions and PFOs, for example due to co-segregation of closely situated genes for PFO and for migraine or for a pro-thrombotic tendency in the case of stroke, is unlikely because other right-to-left shunts, such as pulmonary arteriovenous shunts and atrial septal defects, are also associated with these conditions. For example there is a 53% prevalence of migraine with aura in people who have hereditary haemorrhagic telangiectasia,¹ in which pulmonary arteriovenous fistulae are common and decompression illness risk is high in divers with pulmonary shunts. The observation that individuals with migraine have an increased risk of stroke, decompression illness and transient global amnesia is probably because migraine is an indicator of increased prevalence of a right-to-left shunt.

The magnitude of the shunt across a PFO is determined by the size of the defect in the atrial septum, the mobility and compliance of the septum primum flap covering the defect, the pressure gradient between the right and left atria and atrial flow characteristics. Pressure gradient and atrial flow characteristics will vary with posture, respiration and activities. However, generally a large physiological shunt (as judged by passage of bubbles into the left heart on contrast echocardiography or similar tests) corresponds with a large anatomical defect in the atrial septum.

The incidence of stroke and decompression illness and prevalence of migraine are related to the size of the shunt and hence diameter of the defect. Therefore transcatheter closure of a large PFO would seem an obvious secondary preventive treatment. However in many clinical situations there is no consensus on when this should be performed.

Arterial Hypoxaemia

Arterial hypoxaemia is most likely to occur when there is a large PFO and an increase in right atrial pressure relative to left atrial pressure (e.g. with mechanical ventilation, pulmonary embolism, right ventricular infarction, etc.) or when anatomical changes in the chest (such as following pneumonectomy) lead to the platypnoea-orthodeoxia syndrome. In these situations the causal role of a large PFO is obvious, because closure of the PFO immediately improves arterial oxyhaemoglobin saturation. When a PFO is causing arterial hypoxaemia, transcatheter closure is indicated, except when the PFO is decompressing the right heart. In that situation, closure of the PFO may lead to right heart failure.

Paradoxical thrombo-embolism and ischaemic stroke

Clear examples of paradoxical embolism, with ischaemic stroke or peripheral embolism and thrombus straddling a PFO are well described but rare.

Paradoxical embolism is also very likely in the rare patient with a large PFO who experiences systemic embolism and at the same time either pulmonary embolism or deep vein thrombosis. However more frequently paradoxical embolism is presumed in patients with cryptogenic ischaemic stroke (confirmed on CT or MRI brain scans) and a large PFO, in whom thorough investigation excludes carotid stenosis, atrial arrhythmias and structural left heart disease as a source of thrombo-embolism, but in whom there is no definite proof of venous thrombosis.

When there is proven or presumed paradoxical thrombo-embolism, treatment options include reducing the risk of venous thrombosis or transcatheter closure. Trials to determine which of these treatments is superior are in progress, but they require a large number of patients with a very long follow-up to determine superiority of one treatment. The trials are having difficulty in recruiting patients who generally prefer to have a definitive treatment to close their PFO rather than life-long anticoagulation; even though there is no proof that closure is superior to medical treatment in this situation. Both treatments have a rate of recurrent stroke for several reasons. For example, ischaemic stroke has many causes and the initial and recurrent events in an individual patient may be unrelated to a coincidental PFO. Even if paradoxical embolism was the cause of the initial event, as patients age strokes may recur for other reasons. Inadequate control of anticoagulation may be responsible for recurrent events in those treated medically. In those who undergo closure, recurrent events may be from thrombus formed on the left atrial disc of the occlusion device or as a result of increased predisposition to atrial arrhythmias.

Transcatheter PFO closure should only be offered to patients who have had cryptogenic ischaemic stroke if the PFO is large, if other causes for ischaemic stroke have been excluded and if the patient understands the uncertainty surrounding risk of future events.

Decompression Illness

When ambient pressure is reduced significantly following a dive, tissues are supersaturated with dissolved inert gas, usually nitrogen, and bubbles of the gas are liberated. Most of the bubbles form in veins. Many innocuous dives performed by amateur scuba divers liberate venous bubble, which then pass via the right heart to the alveolar capillaries, where the inert gas passes down the concentration gradient into the alveoli. In this way few bubbles pass through to the systemic circulation during routine decompression, just as few if any bubbles pass through the lungs during contrast echocardiography. However a right-to-left shunt across a large PFO will allow venous bubbles to circumvent the pulmonary filter to reach the systemic circulation and embolise tissues.

During standard contrast echocardiography a gas embolus that reaches the systemic circulation usually has no effect because the embolised tissue has a lower partial pressure of nitrogen than the bubble. The nitrogen gas therefore passes down the concentration gradient from the bubble to dissolve in the

tissue and the bubble collapses. However, during decompression when tissues are supersaturated with dissolved nitrogen, the concentration gradient is reversed and nitrogen passes down the gradient from tissue to bubble. This amplifies bubble size causing tissue ischaemia. Nitrogen is relatively lipid soluble, so that during decompression the greatest amounts of dissolved nitrogen are present in lipid rich tissues (neurological tissues and subcutaneous fat). It is because these tissues are most able to amplify embolic gas bubbles, that the most common features of shunt-related decompression illness are neurological and cutaneous.^{2,3}

There are other causes of decompression illness. Lung disease or a rapid ascent can cause pulmonary barotrauma so that gas invades the pulmonary veins. A provocative dive profile may liberate so many venous bubbles that the pulmonary filter is overwhelmed.

Therefore when determining whether a case of decompression illness was shunt-related we need to:

1. Demonstrate the presence of a large right-to-left shunt.
2. Confirm that the manifestations of decompression illness and the speed of onset of symptoms were consistent with shunt-related decompression illness. Consistent features include cutaneous decompression illness after a dive shallower than 50m, cardio-respiratory symptoms or neurological symptoms starting within 30minutes of surfacing, migraine aura after surfacing, or a combination of these symptoms. The presence of joint pain suggests that the decompression illness was not shunt-related, except when pain is experienced in a joint over which there is the characteristic rash of cutaneous decompression illness.
3. Exclude lung disease or a rapid ascent that could have caused gas trapping and pulmonary barotrauma.
4. Analyse the dive profile to ensure that it would have caused venous bubble formation, but not enough gas liberation to overwhelm the pulmonary filter.

Divers who have had shunt related decompression illness frequently have recurrent attacks. The options to prevent recurrence include stopping diving, modifying diving so that only very short and shallow dives which do not liberate venous bubbles are performed or to have transcatheter closure of the shunt when possible. (Transcatheter closure is the only option for commercial divers, because very restricted diving is not practical.)

In individuals who have paradoxical thrombo-embolism, right-to-left shunts are almost invariably atrial shunts (across a large PFO or an atrial septal defect). This is not true for divers with shunt related decompression illness. Though the majority of shunts are atrial shunts, a significant number are pulmonary shunts. In these cases the shunt is usually through many small pulmonary

arteriovenous fistulae. Closing them is not usually possible at this time, although a single large pulmonary arteriovenous fistula can be occluded.

If transcatheter closure of an atrial shunt has been performed in a diver, it is essential that, before return to diving, a repeat contrast echocardiography is performed to exclude a residual shunt capable of allowing significant transit of bubbles.

A small number of observations suggest that decompression illness during sub-atmospheric decompression (e.g. in astronauts on space-walks) are also often associated with a large right-to-left shunt.⁴

Migraine

It has been known for over 60 years that people who have a history of migraine with aura have a considerably increased risk of getting decompression illness when exposed to decompression. People with migraine with aura have an increased prevalence of right-to-left shunts, usually large PFOs.^{5,6} Shunt size is related to prevalence of migraine with aura.⁷ Thus 53% of individuals with a large right-to-left shunt at rest have migraine with aura, compared with 21% of those with a large shunt with a Valsalva manoeuvre and 25% of those with a medium shunt at rest. Those with no shunt or only a small shunt have rates of migraine similar to those in the general population.

Most studies show that people who have migraine without aura have rates of shunts that are slightly higher than the rates in control groups but the differences are not significant. It is possible that the studies were underpowered for detection of a small difference.

A number of observational studies have reported that when transcatheter closure of a PFO is performed in patients who have had stroke or decompression illness, those patients who had migraine before the procedure usually have an improvement in migraine symptoms after the procedure.⁸⁻¹⁴ Some patients report no recurrence of migraine, though there may be an initial exacerbation of migraine for a few weeks following the procedure, particularly when aspirin is the only anticoagulant given during this period.^{8,15,16} Overall, about 80% of patients who had migraine before their closure procedure report that their migraine had ceased or was improved and about 20% report that their migraine was unaffected by the closure procedure. Improvement appears to occur in those who had migraine without aura as well as those who had migraine with aura.

It is unlikely that the improvement in migraine following transcatheter closure of a PFO is the result of a placebo effect because those who initially reported this had no *a priori* expectation that PFO closure would affect their migraine and because, if this were a placebo effect, it would be the greatest ever reported. However, definitive evidence that closure of large PFOs will improve migraine is sought in the MIST (Migraine Intervention with Starflex[®] Technology) Trial. This multicentre study is a randomised double-blind comparison of transcatheter closure of PFO versus sham intervention. The

trial recruited patients with frequent attacks of migraine (at least 5 days of migraine per month), who had some migraine aura and who had failed to respond to at least two classes of prophylactic medications. They had cardiac assessment to exclude the presence of coincidental cardiac disease. If transthoracic contrast echocardiography showed a significant atrial right-to-left shunt consistent with the presence of a large PFO, they were eligible for randomisation under general anaesthetic to transcatheter closure of the PFO with a STARFlex[®] device or sham procedure. Balloon sizing of the defect was performed during the closure procedure.

In the MIST Trial 60.2% of migraine patients had a right-to-left shunt (16.7% small shunts, 5.1% large pulmonary shunts, 0.7% atrial septal defects and 37.7% large PFOs). The mean PFO diameter in those randomised to closure was 9.2 ± 3.3 mm. It is anticipated the effect of the procedure on migraine incidence in patients in the MIST Trial will be presented at the Annual Scientific Session of the American College of Cardiology in March 2006.

Detection of a PFO

There has been much written about the best way to detect a clinical relevant PFO, but in clinical practice the choice is between transthoracic contrast echocardiography, transoesophageal contrast echocardiography (TOE) and transcranial Doppler with contrast injections. In our opinion, transoesophageal echocardiography is over-rated as a technique for detecting a PFO. This is because we have closed many PFOs that were over 10mm diameter but were missed on TOE by operators who are reputedly amongst the best TOE operators in the UK.¹⁷ Similarly in the MIST Trial transthoracic contrast echocardiography was the techniques used for screening, but TOE performed during the transcatheter closure procedure often failed to show a large PFO until a wire was positioned across the atrial septum. Transthoracic contrast echocardiography is our method of choice. Transcranial Doppler with contrast is sensitive, but does not always allow one to distinguish between a large PFO and a pulmonary right-to-left shunt. This may be less important when investigating paradoxical thromboembolism, when a large right-to-left shunt is almost certainly across an atrial shunt. However when dealing with patients who have decompression illness or migraine, large pulmonary shunts are numerically more important. Misdiagnosis of pulmonary shunts as atrial can lead to patients having an inappropriate attempt at transcatheter closure. The key to reliable diagnosis is getting a lot of experience of the technique, performing it rigorously and auditing and correlating your results with findings at the closure procedure.

Closure of a PFO

There are a number of devices for PFO closure, which are currently approved, and a number of innovative developments being tested. Devices available include STARFlex[®] (NMT), Amplatzer[®] (AGA), Premere[®] (St Jude), PFO STAR[®] (Cardia) and Helex[®] (Gore). The basic design and principles behind each of these devices are similar. Each device consists of two connected discs or plates. A guide wire is used to position the delivery system/catheter in

the left atrium. The left atrial disc or plate is deployed and pulled back against the atrial septum. Then the right atrial disc or plate is deployed, so that the device straddles the septum with one disc or plate either side of the PFO. Closure of the PFO is partly dependent on growth of endothelium over the device. The delivery systems and methods used to deploy the devices are different for each device. The only way to learn how to perform PFO closure is to get practical training with the devices. The device manufacturers are very willing to assist cardiologists to obtain training.

There are no studies comparing the effect of PFO closure with different devices on recurrence rates for stroke, decompression illness and migraine. There are few studies comparing the success rates for closure of PFOs and the procedural and late complication rate with different devices. However it is clear that some rare late complications, such as late erosion of devices into the aorta and pericardium, might be prevented if PFOs could be closed without leaving a device with metal parts in the heart. Promising new technologies being tested include bioresorbable devices. BioSTAR[®] (NMT) has a bioresorbable, drug eluting implant with tissue engineered collagen matrix discs but its nitinol support framework is similar to STARFlex[®]. It is anticipated that eventually an entirely bioresorbable device will be produced. Cierra are testing the PFX[®] radiofrequency closure system. This uses radiofrequency delivered at the PFO to seal the septum primum flap to the septum secundum.

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