Percutaneous closure of the patent foramen ovale: A cardiological perspective

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ABSTRACT

A patent foramen is commonly found in the general population. Evidence exists that a patent foramen ovale (PFO) and atrial septal aneurysm are strongly associated with cryptogenic stroke. Associations with migraine have also been described, but the status of cause and effect is less clear. Management of PFO is controversial and no form of therapy has been properly evaluated. PFO closure devices are readily available and can be safely and effectively implanted percutaneously. Complication rates are low and symptoms are improved in most patients. At present, there is a lack of guidelines for the treatment of PFO and results of prospective randomised trials are eagerly awaited. SAHeart 2010; 7:264-271

INTRODUCTION

Until recently, the patent foramen ovale (PFO) was considered a foetal remnant and of limited clinical importance. It has now been recognised that patency of the foramen ovale results in problems exclusively encountered in adults, especially stroke and migraine. Improvements in methods of closure and diagnosis have become available for clinical practice and focused renewed attention on the risks and management of patients with a PFO.

ANATOMICAL ISSUES

In a healthy population, up to 27% may have a PFO.[1,2] PFOs are anatomically more complex than atrial septal defects and consist of two anatomically and dynamically different components – a thick rigid septum secundum and a thin mobile septum primum.[3] Lack of fusion of these two structures results in a patent foramen. The length of the tunnel formed by this interaction is determined by the extent of overlap, whilst the width (diameter) is determined by the area of non-fusion between these two components (Figure 1). Atrial septal aneurysms are frequently associated with PFOs and may bulge into either the left atrium, right atrium or both atria.

Venous flow is channelled towards the fossa ovalis due to the orientation of the inferior vena cava. A prominent Eustachian valve is commonly observed in the presence of a PFO. This may further direct inferior caval flow towards the fossa ovalis.
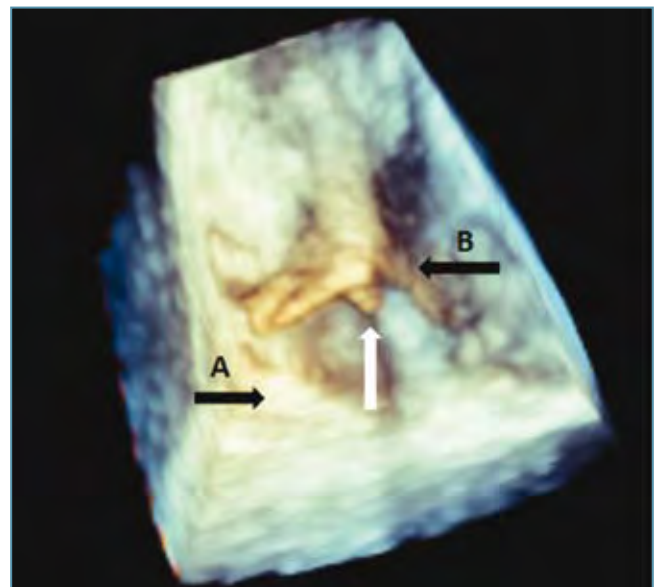

FIGURE 1: Three Dimensional TEE demonstrating PFO anatomy: The thick septum secundum can be seen (arrow A) overlapped by the thin septum primum (arrow B). A guide wire (white arrow) is demonstrated passing through and lifting the long channel, exiting at the opening in the left atrial aspect due to lack of fusion of the septum primum and secundum.
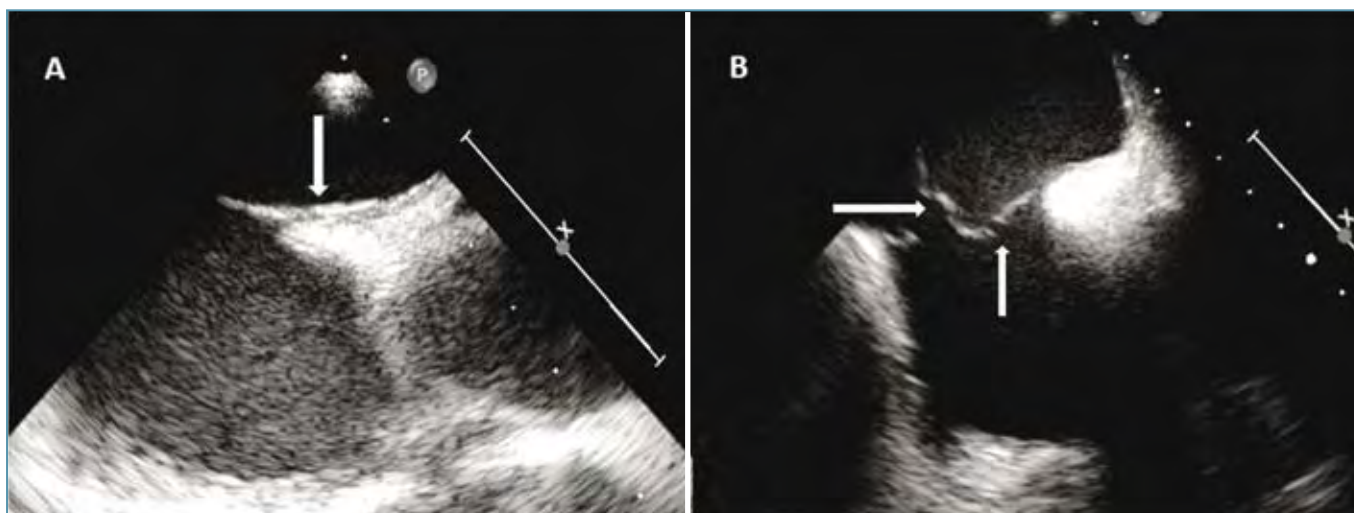
FIGURE 2: TEE images of PFO. In A, a long tunnel-like PFO is demonstrated with a thin septum secundum overlapping (arrow) a thick septum secundum. B shows an atrial septal aneurysm with multiple perforations (arrows).

All of these factors should be taken into consideration during diagnosis and closure of a PFO. Rigid devices not taking the dynamic interaction of the septae into consideration may "splint" the defect and result in either incomplete epithelialisation or residual shunting. Diagnostic consideration should also be given to anatomical and physiological factors. For example, the presence of a prominent Eustachian valve may have an influence on the demonstration of a PFO since contrast injection in the veins of the upper limbs may not yield a positive bubble test due its effect on direction of flow, whilst it may show a large shunt in the same patient if injected via a lower limb vein. Device struts may also be caught in the Eustachian valve, preventing successful closure. The patent foramen ovale is clearly a complex structure and attention should be paid to the anatomical substrate during diagnosis and pecutaneous management of the PFO since it may have a profound influence on risks and outcomes.[4]

DETECTING A PFO

Transthoracic Echocardiography (TTE)

TTE is generally used as a screening test to diagnose PFO and it is important to recognise that a negative TTE does not rule out a PFO. In patients with good echocardiographic windows, anatomical detail of the PFO may be delineated. However, even with harmonic imaging, it has lower sensitivity and specificity (76.5% and 79.4%, respectively) than transoesophageal echocardiography.[5,6]

Using the Valsalva manoeuvre alone or in combination with agitated saline or other contrast agents, results for detection of PFO by means of TTE can be markedly improved.[7-10]

Transcranial Doppler (TCD)

TCD is highly sensitive and specific for the diagnosis of right to left shunts and is the preferred screening tool.[11] TCD does not cause any discomfort to patients and requires no sedation. However, TCD does not differentiate PFO from other causes of right to left shunts (e.g. arteriovenous fistula) neither does it provide any information regarding anatomy or especially, the presence of an atrial septal aneurysm.[12]

Transoesophageal Echocardiography (TEE)

TEE is considered the gold standard for the diagnosis of PFO and delineation of the underlying morphology (Figure 2). It is more invasive than the other methods of detection and patients need to be sedated. Contrast echo, with or without the Valsalva manoeuvre, is helpful in the assessment of a PFO. Bubbles can be seen crossing the PFO during the release phase of the Valsalva manoeuvre as blood kept out of the thorax rushes back into the right atrium. TEE is especially helpful to ensure accurate and safe placement of transcatheter devices. In patients with cryptogenic stroke, it is recommended that TEE should routinely be included in the assessment of such patients since it also allows other cardiovascular causes of stroke to be detected.[13-15]

Overall, there is a lack of standardisation of methods to demonstrate size and significance of PFOs as well as quantification of the shunt. The number of contrast bubbles in the left atrium is sometimes employed, but does not necessarily correlate with the magnitude of the shunt.[16-18] Furthermore, superior caval flow, which is directed towards the tricuspid valve may be prevented from crossing a PFO due to the effect of Eustachian valve streaming which influences the reliability of detection of a PFO's shunting and the injection of echocardiographic contrast into a lower limb vein may prove more accurate.[19,20] Also, since patients are commonly sedated to perform TEE, the Valsalva manoeuvre may be difficult to perform. The classification of atrial septal aneurysm also varies, but tissue movement in excess of 10mm from the septal plane is helpful in the diagnosis.[21-23] Atrial septal aneurysm is frequently associated with PFO as well as other cardiac abnormalities.[24,25] Other imaging modalities such as intra-cardiac echocardiography (ICE) are sometimes employed during implantation of devices, although most operators still prefer TEE.

PFO AND STROKE

Stroke is one of the leading causes of morbidity and mortality worldwide. Cryptogenic stroke accounts for up to 40% of causes of ischaemic stroke and is essentially diagnosed if, after extensive investigation, no other cause of infarction can be identified.[26] The exact mechanism by which PFO causes stroke is ascribed to paradoxical embolism by way of a right to left shunt. The vast majority of studies have reported an increased prevalence of PFO ranging from 31-77% in patients with cryptogenic stroke compared to less than 25% in patients with stroke of known cause.

The presence of an atrial septal aneurysm increases risk: PFO with atrial septal aneurysms occurred significantly more (odds ratio 3.65; 95% CI: 1.64-8.13) in patients than in controls.[27-30] Although this association with stroke has been more convincingly established in patients younger than 55 years of age, recent studies have also demonstrated significant associations in older patients.[13,28,31,32] In addition, a recent publication illustrated that the co-existence of a PFO with atrial septal aneurysm play an important pathogenic role in the severity of white matter lesions in these patients (odds ratio 2.4; 95% CI: 1.11-5.17) compared to stroke patients without septal abnormalities (p = 0.026).[33] The presence of both PFO and atrial septal aneurysm is also a significant predictor of an increased

risk for recurrent stroke – hazard ratio 4.17 (95% CI: 1.47-11.84) with a risk of 15.2% compared to 4.2% in the absence of both.[16] TEE is thus recommended for all patients with cryptogenic stroke to identify PFO or other cardiac causes.[14,15]

RESULTS OF TRANSCATHETER CLOSURE IN ISCHAEMIC STROKE

Currently, due to a lack of appropriate randomised controlled clinical trials, no ideal treatment (medical, surgical or percutaneous device implantation) can be recommended. There is also insufficient long-term follow-up data. Several reports have demonstrated the feasibility of percutaneous closure. Small studies, as well as systematic reviews, showed that recurrence rates for stroke after device closure was reduced to between 0 and 5% (versus 3-12% with medical therapy) with minimal residual shunting.[10,34-36] Interestingly, some of the recurrent ischaemic episodes occurred in patients where no residual shunts could be detected, probably indicating that other underlying mechanisms are involved in the pathogenesis of stroke.

At present, there are no clearly defined guidelines from any professional society and most state that insufficient evidence exists to make a recommendation.[37] The American Heart Association, American Stroke Association and American College of Chest Physicians as a result encourage physicians to participate in ongoing trials (RESPECT, CLOSURE-1, PC-Trial, CLOSE and Gore REDUCE) to resolve the uncertainties regarding optimal care for these patients.[28,38]

MIGRAINE AND PFO

Right-to-left shunts are more prevalent in patients with migraine. Migraine also occurs more commonly in patients with right-to-left shunt lesions. In addition, PFOs have been demonstrated in 40-72% of those with migraine. The odds of a patient with migraine having a PFO are 2.5 times greater than the general population and for migraine with aura 3.2 times greater than those without aura.[39-42] Several retrospective, non-randomised trials suggested benefit following PFO closure. However, the only prospective, sham controlled trial (MIST-I) showed negative outcomes for both the primary and secondary endpoints of improvement of migraine headaches.[43] It was concluded that the role of PFO closure for

the treatment of migraine was unclear. Differences between MIST-I and other studies should be mentioned. Only migraine with aura without history of previous embolic episodes was included, whilst the majority of other studies included patients with migraine and history of embolic stroke. Patients treated in MIST-I all had severe refractory migraine not responding to any other form of treatment and there were controversies regarding the methods of follow-up assessment as well as absence of data regarding the concomitant use of medication.

A current systematic review and meta-analysis of 1 306 patients showed complete cure of migraine after PFO closure in 46% (95% CI: 25-67%) with resolution or significant improvement in 83% (95% CI: 78 -88%).[44] Similar findings have recently been reported and it has been shown that migraine with aura and high pain intensity at baseline were independent predictors of positive response to PFO closure. The study included patients with and without history of paradoxical embolism.[45] There are ongoing randomised trials, including percutaneous closure of PFO in migraine with aura (PRIMA) and the prospective randomised investigation to evaluate incidence of headache with migraine and PFO using the Amplatzer PFO occluder compared to medical management (PREMIUM).

DIVING AND PFO

Neurological decompression events occurring when diving with a PFO are reported to have an odds ratio of 2.6 with PFO present in 60% of patients vs. 36% in controls. A TEE should be performed in divers when no cause is evident after a neurological decompression incident.[46,47] It is recommended that, if a diver wants to continue diving after a PFO is detected following such an incident, other safety measures including the option of percutaneous device closure, could be considered.

PERCUTANEOUS PFO CLOSURE

The initial devices used for closure of PFO were based on versions of atrial septal defect closure devices. Various devices have been employed worldwide, but in South Africa the Amplatzer® (AGA Medical, MN, USA), Atriasept II® (Cardia Eagan, MN, USA) and Solysafe® (Swissimplant AG, Solothurn, Switzerland) devices are available in different diameters (Figure 3). PFO anatomy produces
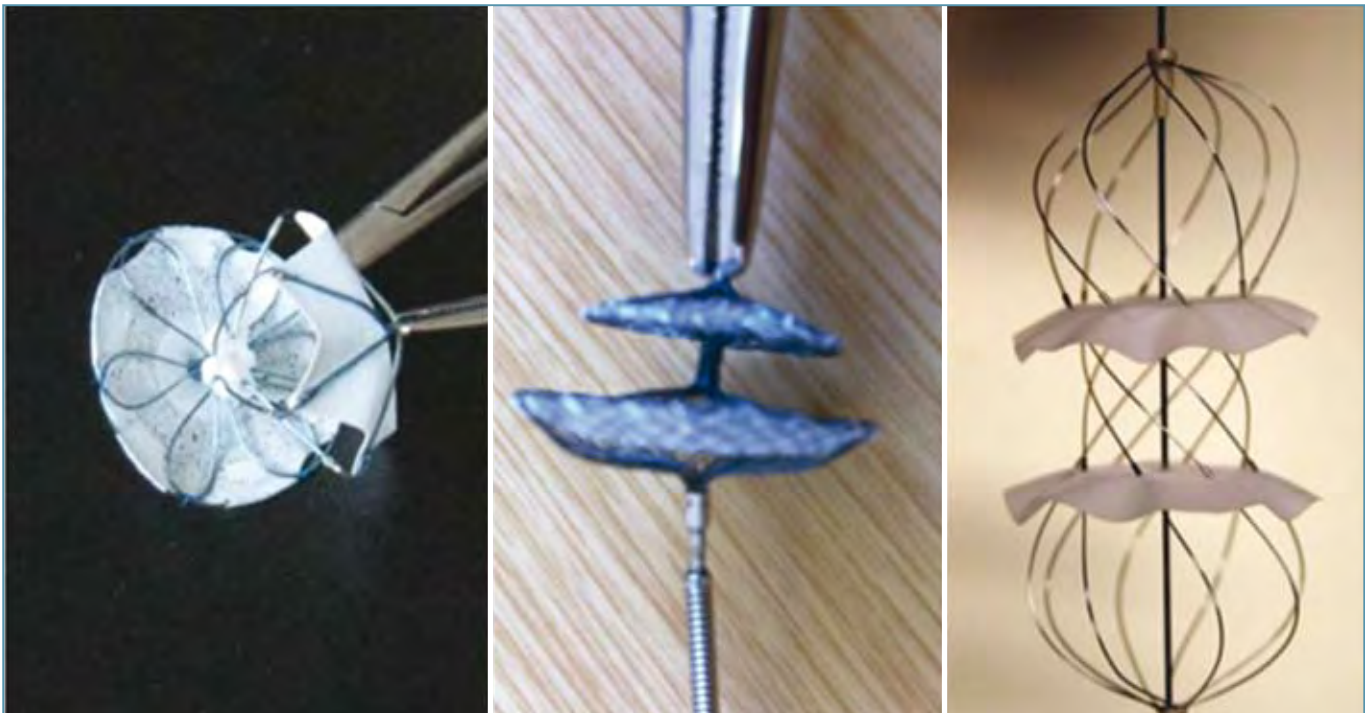

FIGURE 3: PFO closure devices from left to right are: Atriasept II®, Amplatzer® and Solysafe®.

unique challenges and appreciation of these characteristics play an important role in the selection of a device.

PROCEDURE

Technical details have been published but generally it is a relatively simple and quick procedure.[29,35,48-50] In short, percutaneous venous access is gained via the femoral vein and an appropriate long sheath is left in situ after having crossed the PFO into the left atrium. Patients are heparinised and extreme care should be taken to prevent air embolism throughout the procedure. Prophylactic antibiotics are usually given. The procedure may be performed with or without general anaesthesia using one or more of the following for control: fluoroscopy, TEE or ICE. Most operators prefer general anaesthesia and use TEE combined with fluoroscopy. Careful consideration should be given to the morphology of the PFO and surrounding structures when selecting the type and size of a device. Balloon sizing may be required, but this is not generally necessary.[51,52] Presence of atrial septal aneurysms and prominent Eustachian valves may complicate procedures. After selection of an appropriate device, it is deployed in the correct position. Most devices are retrievable and re-useable before release from the delivery mechanism. The device is then released and some are even retrievable at this stage (Figure 4). Patients may be discharged
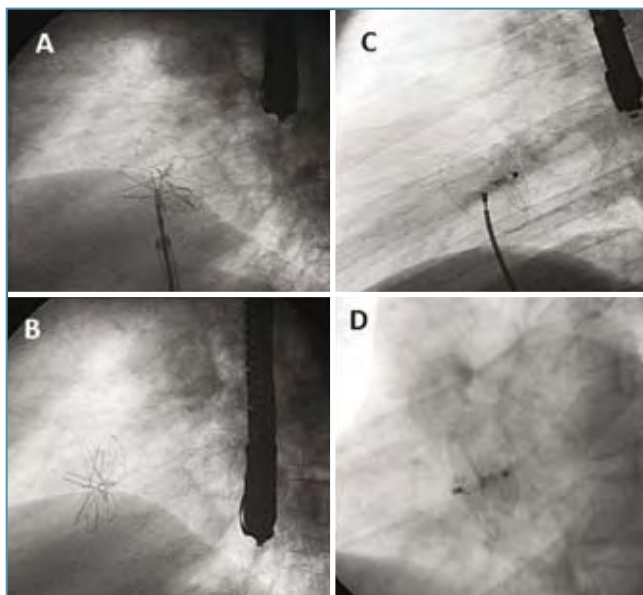

FIGURE 4: Atriasept II® device with cable of delivery forceps still attached (A) and after release (B). Amplatzer® PFO device attached to delivery cable pre-release (C) and after release (D).

on the same day after satisfactory positioning has been confirmed (Figure 5). Clopidogrel is usually prescribed for 4-6 weeks and low dose salicylates for 6 months. Follow-up TEE should be performed 6 months after implantation of a percutaneous PFO device.

Success rates for the procedure range from 98-100%. In experienced centres with experienced operators, complications are uncommon but minor complications (pain, bleeding at site of catheterisation, transient arrhythmias etc.) occur in up to 7.9% and major complications (tamponade, infection, thrombus formation) in less than 1.5% of cases respectively.[10, 41,42, 53, 54] Late erosions into surrounding tissues have been described with all intracardiac devices, but are rare after PFO closure. Residual shunts are common immediately following implantation, but infrequent (5-10%) after 12 months.[35, 55, 56]

MORE RECENT TRENDS

Three-dimensional echocardiography may provide improved assistance during assessment, implantation and follow-up of device closure of defects (Figure 6). New devices are being developed specifically for PFO closure – these are less rigid and bulky and should lead to improvement in closure rates with a reduction in complications.[57] Future devices will probably employ less material and metal and target the specific anatomical defect.

CONTROVERSIES AND FOOD FOR THOUGHT

Percutaneous closure of a PFO can be safely and effectively performed using modern devices. However, the indications for closure are more complex and will be debated for many years to come. Most of the uncertainties are caused by insufficient evidence attributable to the lack of randomised, controlled clinical trials. This is aggravated by the slow recruitment in currently ongoing trials. Literature comparing medical and percutaneous management is not available and current opinion is based on observational studies and case-control reviews with its inherent drawbacks.

Compelling evidence exists that PFO with atrial septal aneurysm carry considerable risk. It is more difficult to quantify this risk in the presence of a PFO. The question of cause and effect is still unclear and therefore double standards in management exist.[58-61] Most
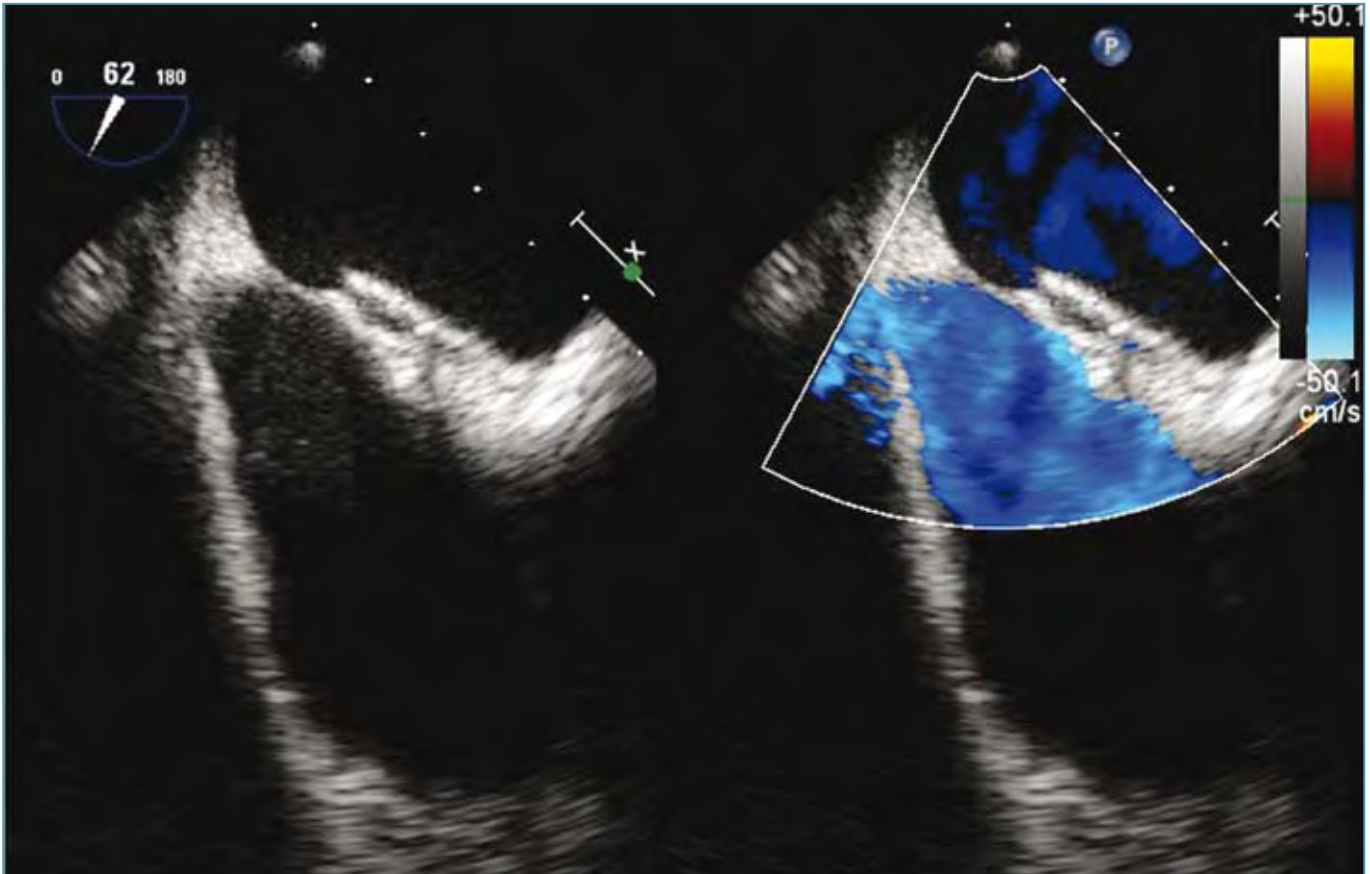
FIGURE 5: TEE showing good position of PFO device with stabilization of atrial septal aneurysm and no residual leaks.

likely, many different mechanisms are involved in causing stroke and migraine in the presence of a PFO and probably PFO closure may benefit only certain subsets of patients. Decisions we make now have an effect upon the future and, as treating physicians, we could end up in difficult situations: We could close defects unnecessarily with the risk of complications while having little effect on prevention of stroke; or alternatively delay closure and face medico-legal risks due to "malpractice" in future years. Add to this a patient who had a stroke and knows that there is a "hole" in his/her heart and one can understand that it makes for an emotional debate.

It is also important to recognise what effects rigid devices may have on intra-cardiac structures. In a thought provoking editorial, McElhinney pointed out that studies have shown aortic regurgitation, erosion and atrio-ventricular block with intra-cardiac devices, sometimes many years after implantation due to the interaction of the devices with the surrounding tissues. He postulated that the
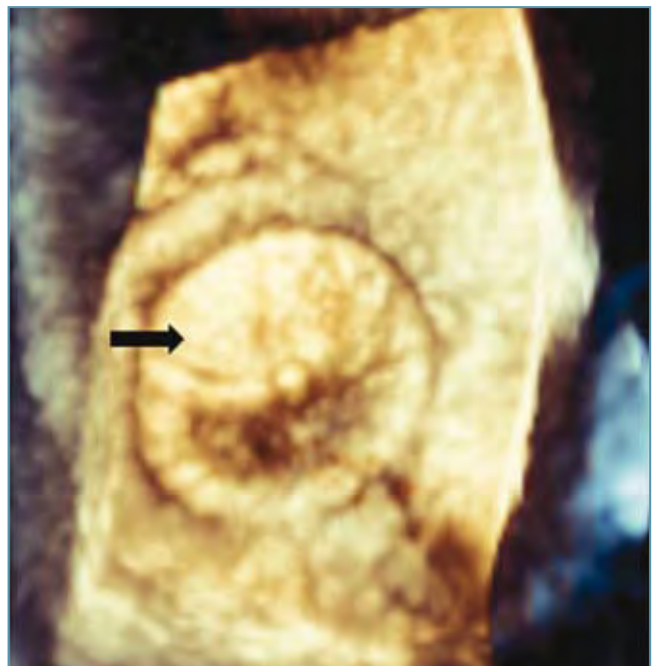

FIGURE 6: Three Dimensional TEE image of PFO closure device: Left atrial disk of closure device in good position against inter-atrial septum.

future of PFO closure may hinge on these considerations more than other.[62]

At present it seems that PFO closure may be of benefit, although unproven, in patients with PFO and atrial septal aneurysm with a history of: cryptogenic stroke (especially if <55 years); recurrent deep vein thrombosis and pulmonary embolism; existence of contra-indications to anticoagulation; large shunts; and in commercial divers. These are only suggestions and not recommendations or guidelines. It also emphasises the need for societies to provide clear guidelines to assist treating physicians and bring ''closure'' to this matter.

CONCLUSION

PFO is a common congenital anomaly in the general population. In contrast to previously held beliefs that a PFO is an innocent anomaly, it has been found to be more prevalent in patients with cryptogenic stroke and certain forms of migraine. No optimal therapy for PFO in these patients, either medical or interventional, has been identified and future clinical management will depend on clarification of the pathogenesis related to these conditions. Percutaneous closure of a PFO is relatively simple. The devices have been shown to be effective and safe. Evidence for best treatment is lacking and results of randomised, controlled clinical trials are eagerly awaited.

ACKNOWLEDGEMENTS

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