REVIEW

Patent foramen ovale and atrial septal aneurysm in cryptogenic stroke

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Up to 40% of acute ischaemic strokes in young adults are cryptogenic in nature, that is, no cause is determined. In more than half of these patients, patent foramen ovale (PFO) is seen along with an increased incidence of atrial septal aneurysm. The commonest method of investigation is echocardiography (preferably transoesophageal echocardiography). On the basis of available evidence, low risk patients are treated with antiplatelet agents and high risk patients with warfarin. There are inconclusive data on the efficacy of PFO closure to prevent stroke recurrence. However, if there is recurrent stroke or intolerance to medical therapy, percutaneous closure is carried out.

Stroke is a leading cause of death and long-term disability worldwide. Most strokes (85%) are ischaemic in origin and tend to occur in persons over 65 years of age. A minority of ischaemic strokes affect younger adults and the cause remains undefined in up to 40% of these younger adults with acute ischaemic stroke.^{1 2}

Patent foramen ovale (PFO) and atrial septal aneurysm (ASA) are known to be associated with so-called cryptogenic stroke, although in the elderly this may be coincidental rather than causal. In this review we have tried to outline the magnitude of the problem, the methods of PFO/ASA detection, various treatment options and areas of uncertainty.

SOURCES AND SELECTION CRITERIA

We reviewed literature listed in PubMed under the headings “patent foramen ovale”, “atrial septal aneurysm” and “stroke” from 1966 until February 2006. We obtained further articles from the references identified in the initial literature review.

PATENT FORAMEN OVALE

The commonest source of potential cardioembolism in young adults with cryptogenic stroke is PFO. PFO is a haemodynamically insignificant interatrial communication present in about 27% of unselected adults.³ It is detected in more than half of young patients undergoing evaluation for so-called cryptogenic ischaemic stroke.⁴

During fetal life the lungs do not receive blood flow. Thus blood returning to the right atrium is shunted through a PFO to the left atrium. Postnatally, the PFO spontaneously closes in about 75% of the population. However, in a proportion of adults PFO maintains a direct communication

between the right and left sided circulation. Given that PFO can be a tunnel-like structure with a possibly stagnant area of blood flow in situ, thrombus formation can occur. Patients with PFO may be susceptible to atrial arrhythmias with possible atrial thrombus formation and PFO can serve as a conduit for paradoxical embolisation.⁵

The association of PFO with stroke was described in 1877 by Cohnheim⁶ in a young woman with cerebral embolism. It was difficult to diagnose PFO in vivo before the advent of echocardiography. However, with the use of echocardiography, a strong association between cryptogenic stroke and PFO has become evident in young patients with stroke.^{4 7–11}

Stroke tends to occur more frequently in older populations, with only 3% of infarcts occurring in patients less than 40 years of age. Therefore, the number of strokes occurring in those older than 40 years of age with PFOs is expected to be greater than in younger patients. Several reports have shown this to be the case,^{9 10} other studies have not.^{11 12} The association between cryptogenic stroke and PFO is well established in young patients but has yet to be firmly established in the older population.

PATENT FORAMEN OVALE AND MIGRAINE

In patients with migraine with aura the prevalence of right-to-left shunt is significantly increased and is similar to that in young patients with cryptogenic stroke. The unresolved question is whether the association is causal or coincidental. Some studies suggest a common biological link.^{13–15} Patients with aura develop hypoperfusion of the occipital cortex and paradoxical emboli seem to have a predilection for this area of the brain.¹⁶ Migraine with aura may be caused by paradoxical microembolisation of air, thrombi or vasoactive neuromediators that are normally filtered and degraded by the lungs.

If one postulates a relationship between PFO and migraine, closure of the PFO should result in an improvement in migraine. The preliminary result of the MIST trial was recently presented and showed that PFOs are six times more common in patients with migraine with aura and that closure of PFO may lead to reduction in headache, although the primary endpoint (complete elimination) of headache was not achieved.¹⁷ However, these results should be viewed with

Abbreviations: ASA, atrial septal aneurysm; PFO, patent foramen ovale; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography

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some scepticism considering the high frequency of both migraine and PFO in general population.

ATRIAL SEPTAL ANEURYSM

An ASA consists of redundant atrial septal tissue bulging into the right or the left atrium. ASA have been found in 1% of consecutive autopsies¹⁸ and in about 4.9% of patients undergoing transoesophageal echocardiography for reasons other than a search for sources of emboli.¹⁸⁻²¹ A significantly higher percentage has been reported in pre-selected patient populations with otherwise unexplained transient ischaemic attack (TIA) and stroke.^{9 22-24} These highly selected control groups may have led to a bias and over-estimation of the true prevalence of ASA in an unselected population. One of the recent studies demonstrated a higher percentage of ASA in patients with cerebral embolism of unknown origin (7.9%) compared to a large matched population-based (thus not pre-selected) control group (2.2%).²⁵

Different definitions for the cut-off point between a mobile and aneurysmatic atrial septum have been used which might partly contribute to the variously reported prevalences.²⁶ There is now general agreement in all definitions that the basal width of an ASA 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.

ASA is rarely an isolated irregularity. In the majority of cases it is associated with other cardiac abnormalities such as PFO and atrial septal defects as well as mitral valve prolapse or atrial arrhythmias.^{27 28} These abnormalities are also possible sources of cardiac emboli and thus it is even more difficult to assess the embolic potential of an ASA independently.

Mattioli *et al* have demonstrated a statistical association between PFO and ASA and have also shown that both morphological abnormalities were independent predictors of embolic events in a multivariate analysis. The association was stronger in a subgroup of patients below the age of 45 years, where 97% of patients with ASAs also had a PFO. However, the low overall frequency of PFO compared to earlier studies makes interpretation difficult.²⁹

The association of ASA and PFO is of great clinical importance because different therapeutic options have been used to avoid recurrent embolic events in PFOs and to circumvent the otherwise necessary life-long anticoagulation.

EVALUATION/METHOD OF DETECTION

Transoesophageal echocardiography is superior to transthoracic echocardiography (TTE) for the detection of potential sources of cardioembolism.³⁰ TTE identifies sources in about 25% of patients with clinically apparent cardiac disease, but its yield in patients without cardiac signs or symptoms is less than 10%. Transoesophageal echocardiography detects a source of cardioembolism in as many as 57% of patients with unexplained stroke.³¹

Typically, agitated saline contrast medium is injected into a peripheral vein during the strain phase of the Valsalva manoeuvre and the atrial septum is imaged during the release phase of this manoeuvre. Intravenous injection of saline mixed with air greatly enhances the diagnosis of right-to-left shunts by TTE or TOE by permitting visualisation of microbubbles in the chambers of the left side of the heart that would otherwise be filtered by the lung capillaries.³² If clinical suspicion is high but a shunt cannot be detected by injecting agitated saline contrast medium into a peripheral vein, the femoral vein should be used.³³

Transcranial Doppler sonography is an alternative method of detecting a PFO and is considered by some to be superior to the use of two-dimensional echocardiographic imaging of the atrial

septum after intravenous injection of saline contrast medium.³⁴ A transcranial Doppler/agitated saline method, in which imaging of the middle cerebral arteries is used to detect right-to-left shunting of microbubbles, is often used in many centres.

RECURRENT STROKE PREVENTION

Various treatment modalities are available for secondary prevention in patients with cryptogenic stroke who on assessment have PFO.

To date no study has randomly assigned patients with cryptogenic stroke and PFO to different therapies. Thus our knowledge is based on observational studies which have used varying definitions to define recurrence of stroke and different criteria to define atrial septal abnormalities. In these studies little has been done to abolish the effects of associated confounding risk factors and adjunctive therapies.

The risk of stroke recurrence in patients younger than 60 years of age with cryptogenic stroke (with subsequent detection of PFO) appears to be low. The Lausanne study showed that the annual recurrence rate was 1.9% irrespective of therapy received.³⁵ In contrast, however, it was shown in one study that patients who had both PFO and ASA had a much higher (15.2% v 2.3% over 4 years) rate of recurrence despite medical therapy (use of aspirin) compared to those with PFO alone.³⁶

Medical therapy

It is uncertain if medical therapies such as warfarin and antiplatelet agents are effective as primary or secondary therapy in preventing stroke in patients with PFO.³⁷ The Lausanne Stroke Registry (cited above) compared aspirin to oral anticoagulation in patients with PFO and cryptogenic stroke. The study investigated the effect of aspirin (250 mg/day) on 92 patients versus the effect of warfarin on 37 patients (with a target INR of 3.5). The annual stroke recurrence rate was 1.9% for a cerebrovascular event and 3.8% for combined TIA and a cerebrovascular event in 3 years of follow-up. No significant difference was found between the aspirin and warfarin treated groups.

In the PFO In Cryptogenic Stroke Study (PICSS), 33.8% of 630 patients found to have a PFO on transoesophageal echocardiography were randomised to either aspirin 325 mg or warfarin (target INR 1.4-2.8). Investigators found no difference in primary end points (stroke recurrence and death) between aspirin and warfarin treated patients with PFO at 2 years.³⁸ This is the only randomised study to compare warfarin and aspirin in patients with PFO. However, it was a substudy of the Warfarin-Aspirin Recurrent Stroke Study (WARSS) and was not designed to evaluate the superiority of an antithrombotic strategy in those with stroke and a PFO.³⁹

The major bleeding risk from medical therapy, particularly from the use of warfarin, is estimated to be 1-2% annually and minor bleeding risk to be 10% to 20% higher in those on warfarin compared with aspirin.^{40 41}

Percutaneous transcatheter closure

Newer percutaneous device techniques to close a PFO have been introduced in the past decade. The effective PFO occlusion rates, defined as no or trivial residual shunt after device deployment, have ranged from 63% to 100%.^{42 43} Recurrent neurological or peripheral embolic events have ranged from 0 to 3.8% per year following device placement.⁴⁴

As with any procedure, operator experience greatly influences outcome. Venous access complications, air embolisation, device embolisation and atrial wall perforation have been reported during device implantation. After implantation, other complications including device embolisation, bacterial endocarditis, thrombus formation and frame fracture and deformity

have been reported. Different closure devices are now commercially available.

Surgical closure

In recent times surgical closure has become rare with the advent of percutaneous PFO closure methods. Studies give conflicting results as regards the safety and efficacy of surgical PFO closure as compared to medical treatment. A meta-analysis of five retrospective studies showed that direct surgical closure may be superior to medical treatment in preventing recurrence, but this difference was stated to be mainly due to superiority over antiplatelet therapy. When compared to warfarin therapy, the difference was no longer obvious.⁴⁵

Homma *et al* described the safety of surgical closure of PFO, but was not able to demonstrate its superiority in preventing recurrence of ischemic events.⁴⁶

In another study (which included patients younger than 60 years of age and had at least two of the following four as selection criteria: i) recurrent cerebrovascular events or multiple ischaemic lesions on MRI; ii) PFO associated with ASA; iii) more than 50 microbubbles counted in the left atrium on TEE; and iv) Valsalva manoeuvre or cough preceding the stroke) there was no recurrent stroke or TIA at 2 year follow-up without antithrombotic treatment.⁴⁷

Similar results were reported by Ruchat *et al*.⁴⁸

Comparison of modalities

There are no direct randomised comparisons of treatment modalities, but there are some non-randomised, unblinded trials. A review of 10 non-randomised unblinded transcatheter closure studies for secondary prevention reported a 1 year recurrence of neurological events of 0 to 4.9% in patients undergoing transcatheter closure compared with 3.8% to 12% in medically treated patients.

In collective analysis there are no convincing data to indicate that the presence of PFO increases recurrent events in medically treated patients.³⁷ Whether PFO closure decreases the event rate remains to be answered conclusively, although some analyses suggest the possible superiority of percutaneous closure compared to medical therapy.⁴⁹

It is important to realise that indirect comparison of medical and percutaneous closure is very difficult to interpret as the inclusion criteria are not uniform and the definition of cryptogenic stroke varies in the different studies. The studies are not randomised or blinded and in some of the studies there

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is a prolonged time period between the index neurological event and percutaneous closure. In addition, the low incidence of recurrence makes it even more difficult to design a study sufficiently powered to demonstrate the efficacy of a particular treatment modality.

RECOMMENDATIONS AND GUIDELINES

The American Heart Association/American Stroke Association has recently published revised guidelines⁵⁰ which state that antiplatelet agents may be used for the prevention of ischaemic stroke or TIA in patients with stroke with PFO and that warfarin may be used in high risk patients (those who have other indications for oral anticoagulation such as those with an underlying hypercoagulable state or evidence of venous thrombosis). Patient choice will need to be addressed, especially when making a decision as many younger patients do not wish to take warfarin.

Insufficient data exist at present to make a recommendation about PFO closure in patients with a first stroke and a PFO and in those in whom medical treatment is contraindicated. PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy.

ONGOING TRIALS/AREA OF FURTHER RESEARCH

Further studies are needed to establish the possible superiority of one treatment modality over another, including differences, if any, between the antiplatelet agents and anticoagulants.

Currently there are three, ongoing, randomised studies in the United States comparing the efficacy of percutaneous closure with medical therapy: the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial, the CLOSURE I trial and the Cardia PFO trial. Of note, in all trials, patients randomised to the percutaneous arm also received medical therapy for a variable period of time.

MULTIPLE-CHOICE QUESTIONS (TRUE (T), FALSE (F); ANSWERS AFTER THE REFERENCES)

1. The association of cryptogenic stroke and PFO/ASA is most likely to be found in the following patient groups:
 - A. Elderly patients

Key points

- The cause is unknown in up to 40% of acute ischaemic stroke
- PFO is detected in more than half of young patients with cryptogenic stroke
- A higher percentage of ASA is reported in cryptogenic stroke
- Echocardiography (preferably transoesophageal) is the most commonly used method of investigation
- There are no convincing data to indicate that medical treatment fails to prevent stroke recurrence
- Data are inconclusive on the efficacy of PFO closure to prevent stroke recurrence
- Low risk patients should receive antiplatelet therapy
- High risk patients should receive warfarin therapy
- Recurrent stroke/failure/intolerance to medical therapy should be treated with percutaneous closure

- B. Young patients
 - C. Diabetics
 - D. Patients with hypertension
2. It is difficult to establish a direct relationship between ASA and cryptogenic stroke because
 - A. ASA size is usually too small
 - B. ASA has too many anatomical variants
 - C. Studies rarely show statistical significance
 - D. It is commonly associated with other confounding cardiac abnormalities
 3. The following investigations are not done to diagnose a PFO:
 - A. TOE
 - B. TTE
 - C. Carotid Doppler sonography
 - D. Transcranial Doppler/agitated saline
 4. Studies have shown no significant differences in the therapy of patients with PFO and cryptogenic stroke between:
 - A. Heparin and aspirin
 - B. Heparin and warfarin
 - C. Warfarin and aspirin
 - D. Aspirin and clopidogrel
 5. According to the AHA/ASA guidelines warfarin should be used in patients with:
 - A. An underlying hypercoagulable state
 - B. Intolerant to heparin
 - C. Evidence of peripheral vascular disease
 - D. Evidence of aspirin resistance

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ANSWERS (F, FALSE; T, TRUE)

1. (A) F (B) T (C) F (D) F
2. (B) F (B) F (C) F (D) T
3. (C) F (B) F (C) T (D) F
4. (D) F (B) F (C) T (D) F
5. (E) T (B) F (C) F (D) F

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