



The incidence of peripheral arterial embolism in association with a patent foramen ovale (right-to-left shunt)

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DECLARATIONS

Competing interests

None declared

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Ethical approval

No ethical approval was required as this study was an audit, and the agitated saline study was performed for clinical reasons, as part of the patients' investigations. An authorization letter was acquired from the head of the audit department to study the patients with peripheral arterial embolism. Consent forms were completed by those

Summary

Objectives The aim of this study was to examine a cohort of patients who had suffered an arterial embolism to see whether a patent foramen ovale (PFO) was an identifiable cause.

Design This study was conducted in two parts; a retrospective limb involving an audit of patient records over a period of 10 years, and a prospective limb including selected patients from that audit to search for a PFO using an agitated saline test with transcranial Doppler ultrasound monitoring of the anterior cerebral artery. Data on patients with peripheral vascular disease were collected using a structured questionnaire.

Setting A clinical vascular department. All patients were seen in the vascular outpatients clinic.

Participants Patients who had been identified from a retrospective search based on the headline diagnosis of arterial embolus. Collected data on the 71 patients revealed that 75% had predisposing factors for DVT, 70% were male smokers, and 84.4% had a significant past history of vascular symptoms.

Main outcome measures Whether or not patients identified as having a possible PFO actually had one on objective testing with transcranial Doppler assessment of the cerebral circulation with an agitated saline solution.

Results Fifteen patients who were suspected of having a PFO were selected from these 71 patients; 12 of these were found to have no PFO on testing, and three had already undergone a percutaneous PFO closure.

Conclusion The incidence of a PFO in this small study group is no higher than that found in the general population (3/15, 20%). There was high prevalence of male smokers with associated predisposing factors leading to a DVT.

patients who were
involved in the
transcranial Doppler
with agitated saline
tests

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All authors
contributed equally

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Reviewer

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Introduction

A patent foramen ovale (PFO) is an inter-atrial communication recognized since the time of Galen.^{1,2} In 1564 Botallo described the presence of a PFO at birth,¹⁻³ and it is still sometimes referred to as the foramen of Botallo.^{1,2} In 1877 Cornheim described a paradoxical embolus related to a PFO.^{1,2} Patients with a PFO have specific characteristic clinical and ECG findings which may sometimes be altogether absent.² There may be an ejection systolic murmur, there may be fixed splitting of the second heart sound, and there may be non-specific findings of right heart failure. The ECG may reveal a prolonged PR interval, occasional atrial fibrillation and, most specifically, incomplete right bundle branch block. Some patients may present with a history of stroke or a transient ischaemic event of undefined aetiology.^{1,2}

The foramen ovale is a slit-like opening in the atrial septum at the site of the foramen secundum of the septum primum. The left atrial pressure rises shortly after birth and the flap is lightly pressed against the septum secundum and closes the foramen ovale functionally.² Patency of the PFO has been identified as a potential risk factor for paradoxical embolism potentially followed by cerebral or peripheral ischaemic events.⁴ Although the underlying mechanism by which PFO accounts for the phenomenon is not entirely clear, the trans-septal passage of emboli from the right to the left-sided chambers of the heart appear to play an important role.^{4,5} Moreover, 4.2% of patients with a documented PFO and previous embolism are at increased risk of recurrent thromboembolic events even under therapeutic anticoagulation.⁴

Hoffman *et al.* suggested that anatomic patency may persist for several months after birth and 50% of all infants have a probe-patent PFO at the end of the first year of life,² and although this figure falls with age, 30% of the adult population probably have a PFO.

Ordinarily, a left-to-right shunt will cause no problems, but a right-to-left shunt, if large enough, will cause a low arterial O₂ tension (hypoxia) and severely limited exercise capacity. In deep-sea divers there is a risk of paradoxical embolism of gas bubbles (passage of bubbles into the arterial circulation) which form in the

majority of divers in the venous circulation during decompression. Blood can flow in both directions within intra-atrial shunts at various phases of the cardiac cycle and some experts feel that a large atrial septal defect or PFO is a contra-indication to diving.

The average size of a PFO increases from a mean of 3.4 mm in the first decade to 5.8 mm in the 10th decade of life.^{1,2,4} The larger the degree of inter-atrial shunting, the greater the incidence of subsequent transient ischaemic attack or stroke.^{1,2} Depending on the criteria used for diagnosis and the technology used for cardiac assessment, the prevalence of PFO in the healthy population is approximately 20–25%.^{6,7} On the basis of prevalence, it is estimated that approximately 60–70 million Americans have a PFO.⁸ Thus the detection of a PFO during the evaluation of a patient with stroke is not a surprising finding and the frequency of PFO detection in these patients can be as high as 40–45%.^{9,10} PFO is now detected in 10–15% of the normal population using contrast echocardiography. Postmortem studies in otherwise normal hearts have shown a high (27%) prevalence of PFO. The prevalence found in autopsies among stroke patients is even higher (40%).^{2,11,12}

With increasing evidence that a PFO is the culprit in paradoxical embolic events, paradoxical embolism through a PFO should be strongly suspected in a young patient with cryptogenic stroke and the relative importance of PFO is being re-evaluated.^{1,13,14} The clinical diagnosis of paradoxical embolism is almost always presumptive and is suspected in patients who have a venous thrombus, a right-to-left shunt and evidence of arterial embolism.¹⁵ A definite diagnosis of paradoxical embolism is established when a thrombus is seen traversing the shunt.¹⁵ Deep venous thromboses are found with variable success in patients suspected of paradoxical embolism, and the prevalence of DVT ranges from 9.5% to 88% depending on the timing and methods used for diagnosis.¹⁵

It was documented in a recent investigation that the prevalence of a right-to-left shunt was significantly higher in patients suffering from migraine with aura than in healthy controls and similar to that found in young patients with stroke.^{16,17} A recent study revealed that a

right-to-left shunt can occur through a PFO in subjects with obstructive sleep apnoea syndrome during periods of nocturnal apnoea if the apnoea length is longer than 17 seconds.^{18,19}

Echocardiography is a necessary tool for the diagnosis of PFO, which can be diagnosed by the use of either colour flow Doppler or an intravenous agitated saline contrast study. This is performed after obtaining optimal visualization of the atrial septum using transthoracic or if necessary, trans-oesophageal echocardiography.^{1,20} A trans-oesophageal echo provides better visualization of the atrial septum and is therefore more sensitive than trans-thoracic echo for detecting PFO, but it is significantly more invasive and unpleasant for the patient.^{1,21}

Bilateral transcranial Doppler ultrasound (TCD) can be used to assess a right-to-left shunt, by monitoring both middle cerebral arteries during normal ventilation and during a Valsalva manoeuvre according to the Consensus Meeting of the European Society of Neurology.¹⁶ The technique used is described below.

Right-to-left shunting is graded in consensus by an experienced cardiologist and radiologist as follows: Grade 0 – no contrast agent passed from the right to the left atrium; Grade 1 – 3–9 microbubbles passed from the right to the left atrium; Grade 2 – 10–29; and Grade 3 – >30 microbubbles.^{22,23} In 76 healthy volunteers, a trans-thoracic echocardiographic study using a well established, agitated saline contrast technique found that the prevalence of right-to-left shunting through a PFO was 5% when subjects were at rest and 18% when subjects performed a Valsalva manoeuvre.⁶

When a PFO is found in association with an otherwise unexplained neurological event, there is general agreement that the patient should be treated with anticoagulation, and in some cases that the PFO should be closed. Medical treatment consists of the administration of warfarin with or without aspirin to prevent stroke recurrence. Surgical PFO closure using double continuous suture results in no recurrence of neurological events during a follow-up period of 1–4 years but it requires a thoracotomy and cardiopulmonary bypass.^{24,25} Percutaneous closure using a deployable device manoeuvred into the PFO under fluoroscopic guidance is a much preferred option.²⁶

Methods

Data were collected retrospectively over a 10-year period from 1996 to 2006 from patient records at the London Chest Hospital, Royal London Hospital and St Bartholomew's Hospital. Patients with arterial emboli were identified using this headline diagnosis given on the hospital computer database. Medical records were obtained and were then studied in more detail using a notes questionnaire which included questions about the main presenting complaint (such as peripheral arterial embolus or stroke), whether there was a predisposing factor for DVT, a congenital cardiac abnormality, and a past history of bleeding disorder, liver disease, previous stroke or diabetes. The existence of previous investigations such as a CT/MRI scan, transcranial Doppler, trans-oesophageal echo (TOE) or a duplex scan for a DVT and most importantly if a transcranial Doppler test with agitated saline was carried out to identify a right-to-left shunt was also recorded.

Based on the above information 15 patients were identified from the original 71 and some of these were examined in more detail as a prospective study. Seventy-one patients were found to have had an arterial embolus, and 15 of these were thought from the clinical findings to have a PFO.

All patients diagnosed with peripheral arterial embolism, thrombosis, and stroke of undetermined origin, on the basis of the above clinical findings and investigations, were considered in this study. An agitated saline test with transcranial Doppler ultrasound was carried out on those patients in whom a right-to-left shunt was suspected. Patients aged under 15 years, patients with acquired cardiac disease, and patients with known congenital heart disease were excluded.

Transcranial Doppler protocol

The transcranial Doppler¹ and agitated saline test was performed in outpatients using a standard protocol with written informed consent. Agitated saline was injected via an arm vein and the middle cerebral artery was insonated during a Valsalva manoeuvre. If a microbubble storm was detected the study was deemed positive. The process involves the study of blood flow in the middle cerebral artery prior to and after a

peripheral venous injection of agitated saline. A cannula is placed in an antecubital vein and connected to a three-way tap which connects two 10 mL syringes, one of which contains normal saline and the other of which contains air. The air and the saline are mixed by vigorous alternate movements of the plunger of each syringe and when the saline is full of microbubbles the three-way tap is adjusted and the saline is injected into the circulation.

The patient performs the Valsalva manoeuvre (VM) for 5 s, i.e. forced expiration against a closed glottis. The middle cerebral artery is located using a 2 MHz ultrasound probe. Recordings commence at baseline, followed by two further recordings during the VM or during coughing. The first recording is done at baseline followed by two further recordings during VM or coughing. The test is positive if a microbubble storm is detected during any of the recordings.

This process is outlined below:

- Time 0–3 s: 10 mL agitated saline is injected;
- Time 5 s: patient performs a VM/coughing manoeuvre for 5 s;
- Time 3–40 s: observation for microbubbles, which if noted, the test is positive and complete;
- Time 120 s: if no microbubbles, the test is negative and complete.

Transcranial Doppler (TCD) with agitated saline testing has been shown to be more sensitive than echocardiography imaging in order to detect the presence of a right-to-left shunt.²⁷ TCD has been reported to have a 92.85% sensitivity and 82.35% specificity as compared to transthoracic echocardiography for the diagnosis of PFO.²⁸

Results

An initial search of records based on the term 'paradoxical embolus' generated a list of about 900 patients. A refined search of these records using the search term 'peripheral arterial embolism' generated a shorter list of about 450 records. Combining the search terms 'right to left shunt' and 'peripheral arterial embolism' cut the number of records down to 71, and 15 of these were thought likely to have a PFO,

based on a filtering questionnaire applied to the notes. Of the remaining 15 patients, three had previously had a PFO closed using a percutaneous device.

The original 71 patients were analysed for epidemiological data on the aetiology of arterial embolus.

Of the 15 patients selected from the original 71 thought to have a PFO, the 12 who had not had a closure device fitted were invited to attend an out-patient clinic for an agitated saline test. In this study, only five patients could be traced and studied. This formed the prospective part of the study.

Retrospective data results

Of the initial 71 patients, 44 were men and 27 were women. The mean age was 65.1 years. One of the patients was a scuba diver. The commonest site for an embolus was in the leg (38) followed by the foot (9) and the arm (6). There was only one stroke.

The duration of symptoms varied; 13 patients had been suffering for less than a week, 14 for between a week and a month, and 41 for more than a month. Two patients were not documented. A higher percentage of the patients had a recurrence of signs and symptoms and around 34% had no recurrence after treatment given.

There were a number of predisposing factors which included recent surgery (16), hypercoagulability (14), immobilization (12) and previous DVT (10). No predisposing factor could be found in 20 patients; 75% had an identifiable predisposing factor.

Twenty-one percent had a history of diabetes mellitus and 7% had had a stroke; 67.6% of the selected patients were smokers and 38% consumed alcohol – there was no clear record of the amounts; 57.7% of the patients had undergone tests for a hypercoagulable state.

Thirty-two patients underwent an investigation to rule out DVT; this consisted of a duplex ultrasound in all patients, with an additional Venogram if the results were equivocal; 23.9% of the patients had this done within 7 days, two between 8–10 days and five after 10 days. The majority underwent an angiogram or an angioplasty. Nine percent of the patients underwent a

TOE. Around 4% had a transcranial Doppler, ECG, arterial duplex scan and angiogram.

As far as treatment is concerned, 50% underwent surgical treatment for removal of the embolus, 30% were treated conservatively and 17% were treated conservatively initially and then proceeded to surgery. There was one death reported

Prospective data results

From the 71 patients included in the study as having suffered a peripheral arterial embolus, 15 were selected because they were thought to have a right-to-left shunt. These were seen as outpatients and a transcranial Doppler agitated saline test was carried out. Only five of the 15 patients were available for this investigation. Three had already had a percutaneous closure of PFO and seven were not contactable. The test procedure was explained and consent was taken. The test result was documented on a standardized form. All five tests were negative and no right-to-left shunts were found.

Discussion

Statement of principal findings

The incidence of a PFO in this small study group was found to be no higher than that found in the general population (3/15, 20%). There was a high prevalence of male smokers with associated predisposing factors leading to a DVT. Seventy-five percent of patients had predisposing factors for DVT, 70% were male smokers and 84.4% had a significant past history of vascular symptoms. The study showed that PFO may not be a major or direct cause of paradoxical embolism, even though there is direct evidence dating back to 1877 that this might be the case.²⁹

Strengths and weaknesses of the study

The main advantage of this study was that comprehensive data was collected over a 10-year period from 1996 to 2006 and appropriate patients were identified after detailed scrutiny. Informed consent was obtained and agitated saline testing, which is a sensitive test that provides rapid results in a minimally-invasive and cost-effective

manner. The major weakness of this study is the fact that a very small sample size was obtained. This does in fact suggest that the number of symptomatic PFOs compared with the total number in the population is small, and this is discussed below.

Strengths and weaknesses in relation to other studies

Many studies show that there is a high prevalence of PFO in approximately one-quarter of the general population.³⁰ Age does not play much of a role in the formation of an embolus and is not a predictor of PFO in patients with cerebral ischaemic events.¹¹ In the present study the mean age was 65.1 years and none of them were found to have a PFO (RLS). The three patients who we reviewed who had already had PFO closures were all below 55 years of age. Also there have been studies showing that ASA and PFO are frequently observed with cerebral ischaemic events especially in patients who are under 55 years old.^{31,32}

Paradoxical embolism through a PFO is a recognized cause of stroke.^{23,33} In our small study, very few patients had suffered a properly diagnosed stroke. A study from Minnesota, USA³⁴ concluded that 'Patent foramen ovale is not a risk factor for cryptogenic ischaemic stroke or transient ischaemic attack in the general population'.

There was one occupational scuba diver included in our study, though he did not show any signs of PFO. There are studies which show that PFO increases the risk for decompression illness by a factor of up to five times due to the increase in intrathoracic pressure.³⁵⁻³⁷ These subjects should minimize the load of tissue nitrogen during dives or if this is not possible they should give up diving.³⁷

There has been much debate on the ideal investigation to rule out a PFO or other right-to-left shunt. Contrast transoesophageal echo, a semi-invasive technique, has been regarded as the gold standard for the detection of PFO.^{38,39} In the present study 9% of the patients underwent TOE. Doppler, TTE and TOE with agitated saline contrast were performed on just one patient. Recent studies show that c-TTE with second

harmonic imaging and c-TOE are equivalent in sensitivity.^{39–41} The same study showed that c-TOE was not perfect for the diagnosis as sedation is used, hindering the Valsalva manoeuvre;²⁴ which is a safe and useful technique for the detection of a PFO.⁴²

Contrast transcranial Doppler (c-TCD) has been found to be very sensitive in the detection of a RLS,³⁹ and when compared to c-TOE its sensitivity appears to be high.^{39,43,44} In the present study we found around 7% who had had a simple TCD and 12 patients were selected on whom a TCD with agitated saline was carried out. One study showed that it was as sensitive as c-TOE.^{45,46}

Meaning of the study: possible mechanisms and implications for clinicians or policymakers

This small study showed that a PFO may not be a major cause for patients who have suffered an arterial embolism. It also showed that male smokers probably have a higher incidence of paradoxical embolism in the lower limbs with predisposing factors leading to a DVT.

An embolus can be found anywhere in the circulatory tree but half the patients in the present study had a leg embolus. Sixty-three percent of patients had recurrence of symptoms which suggests that regular check-ups are necessary and definite treatment, either medical or surgical, is necessary.

Many had predisposing factors for DVT, such as a hypercoagulable state or recent surgery. It is presumed that the mechanism for PFO-related systemic ischaemic events is paradoxical embolization of thromboembolic fragments originating from the venous tree.⁴⁷ Hence paradoxical embolism could be a risk of DVT. Deep venous thrombosis was detected in nearly 10% of patients with PFO as the sole identifiable cardiac risk factor and it was suggested that phlebography should be performed in patients with medium or large interatrial shunts if a paradoxical embolism is suspected.⁴⁸

It was found in the present study that 68% of our patients were smokers and around 40% of the patients drank alcohol. Smoking, diabetes mellitus and a positive family history are all moderate risk factors for venous thromboembolism.⁴⁹

A positive finding of the signs of postphlebotic limb is often found on examination and here 85% of our patients exhibited this. Investigations for thrombophilia should be carried out and in our retrospective study of 71 patients we found that only half of the patients had undergone this investigation.

Of the 71 patients in the retrospective study one-quarter were treated medically and half were treated surgically while 17% had both forms of treatment. One patient died before treatment could be started. Percutaneous closure of PFO is a minimally invasive procedure, safe, effective in the prevention of recurrent strokes, avoiding lifelong anticoagulants and also cures migraine to some extent.²⁶

Future proposals

The conclusion of the present study was a negative result; PFO may not be a major cause of undiagnosed paradoxical arterial embolism; the incidence of PFO in our patients was the same as in the general population.

Future studies in the form of large prospective multicentre trials are required which would involve the investigation of all arterial embolus patients attending an Emergency Department for the presence of a right-to-left shunt.

Conclusions

There is a suggestion that the incidence of PFO (right-to-left shunt) in patients with peripheral arterial embolism is increased, but the results of our small study show that the incidence is much the same as it is in the general population. Therefore, it appears that PFO may not be a major cause of undiagnosed peripheral arterial embolism.

Our results conform to the accepted incidence of PFO at an estimated percentage of 25–30%^{2,29,33} in the general population.

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