

# Patent foramen ovale and the risk of stroke: smoking gun guilty by association?

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Between 15–20% of cases of brain infarction involve patients under the age of 55 years—that is, 150 000 to 200 000 patients each year in Europe. The main causes include cardiac valve disease and dissections of extracranial arteries (accounting for up to 20% of cases). In this age range, rare causes of arteriopathies may be found more frequently than in older stroke patients. Their mechanism is either inflammatory disease, infectious, metabolic, or toxic. Atherosclerosis accounts for 10% of cases. Over 150 causes of stroke have been listed. However, despite a thorough evaluation, the cause of the stroke remains unknown in up to 50–60% of cases in patients younger than 55 years.

In this group, transoesophageal echocardiography (TOE) shows inter-atrial septal abnormalities in 55–60% of cases. The same abnormal septum is observed in 20% of the normal population. However, when present in a patient with a stroke of unknown cause, is this abnormality responsible for the stroke or the marker for the true cause of stroke? For example, having yellow nails is statistically associated with lung cancer, but does not mean that yellow nails cause lung cancer.

## PFO AND STROKE: A STATISTICAL ASSOCIATION

In 1988, Lechat and colleagues<sup>1</sup> performed transthoracic echocardiography (TTE) with contrast micro-bubble injection and showed that patients with stroke of unknown cause more frequently had PFOs than controls. Since then, numerous studies concurred with this result and have been summarised in a meta-analysis (fig 1).<sup>2</sup>

In a study using TOE in 100 patients and 55 controls younger than 55 years, we found that a PFO was present in 43% of patients, 56% of patients with brain infarction of unknown cause, and in only 18% of controls (odds ratio (OR) 3.9, 95% confidence interval (CI) 1.5 to 10).<sup>3</sup> The statistical association was even stronger in cases with an association between PFO and atrial septal aneurysm (ASA).<sup>3</sup>

## CAUSAL LINK OR CONFOUNDING FACTOR?

Whether or not a patient recovers from a stroke, possibly with a severe handicap, it is tempting to let him or her believe that the cause has been identified and that treating it will avoid a recurrent stroke. However, in the presence of a PFO or ASA, given the uncertainty of their causal link with stroke, the potential mechanisms underlying the stroke are always delicate to explain to the patient.

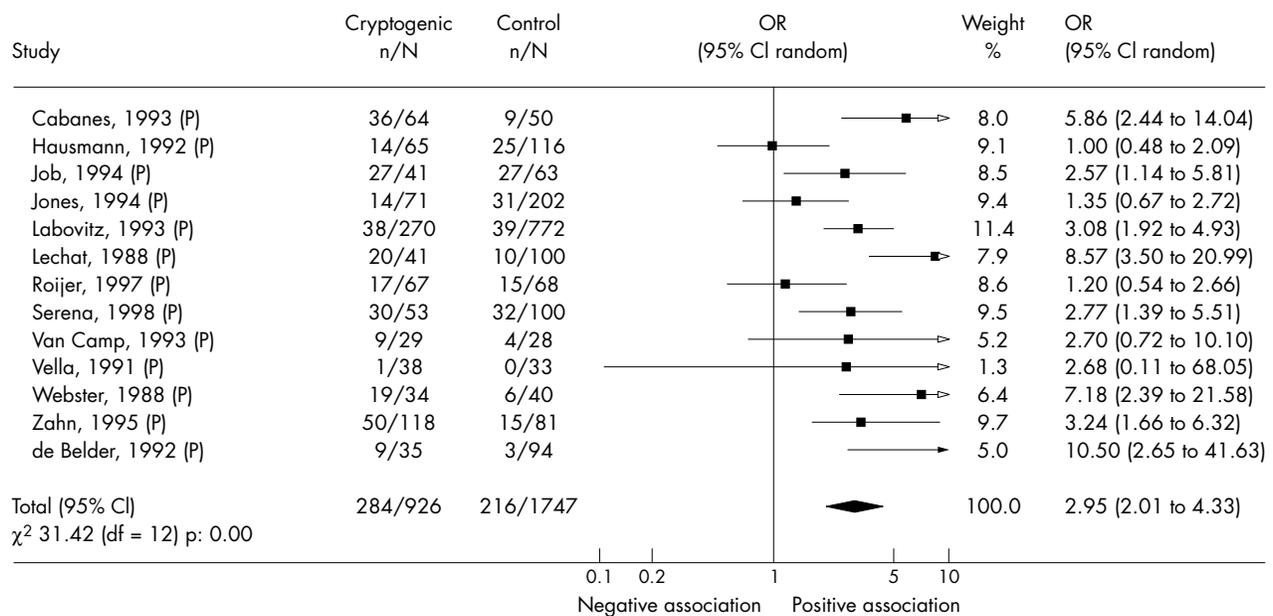
There are several possible scenarios:

- The PFO is associated with a deep venous thrombosis, which occurred before the stroke, sometimes associated with (or preceded by) a pulmonary embolism or pulmonary hypertension. In this case, the hypothesis of a paradoxical embolism is strong. This is rare in practice.
- The PFO is associated with a mural thrombus formed locally in the atrial septum within the conduit of the PFO. Sometimes TOE examination can image this floating

thrombus in both left and right parts of the atrial septum; this is also very rare, and ascertains the PFO as the responsible donor source of emboli.

- The PFO is isolated or is associated with ASA, without any other abnormality. In this case there are several hypotheses:
  - It may be a paradoxical embolism with an occult deep vein thrombosis; it is indeed common to have a pulmonary embolism without a diagnosis of deep vein thrombosis. The deep vein thrombosis could be located in the pelvis, as recently suggested by a magnetic resonance angiography study. However, a Valsalva manoeuvre is mandatory to allow a paradoxical embolism. In our study, such a Valsalva manoeuvre had the same low frequency in stroke patients with or without a PFO.<sup>4</sup> Moreover, if the paradoxical embolism hypothesis would be valid, these patients must have the same coagulation profile as patients with pulmonary embolism or deep vein thrombosis regarding the frequency of, for example, protein C/S deficiency, factor V Leiden, or prothrombin gene mutations, which is not the case (patients with stroke and PFO have the same frequency of these mutations as in the general population and well below the one found in a typical deep vein thrombosis population).
  - A thrombus may form in the conduit of the PFO, as surgeons frequently observe fibrin deposits there.
  - Atrial arrhythmia may play a role in causing thrombus formation and brain emboli in the presence of atrial septal abnormalities. Besides transcardiac paradoxical emboli and thrombus formation within the atrial septum, atrial arrhythmia is another hypothesis for explaining the causal link between PFO or ASA and brain infarction of unknown cause. We found a significant association between atrial vulnerability and the presence of PFO, ASA, or both.<sup>5</sup> Up to 58% of patients with atrial septal abnormalities had atrial vulnerability as compared with 25% of patients without atrial septal abnormalities. Transient atrial arrhythmias may occur in the presence of PFO or ASA and the higher embolic risk may be caused by a greater potential for paroxysmal atrial fibrillation.<sup>5</sup> In animal models mechanical atrial stretching induces cellular action potential modifications of the atrial myocardium with shortening of atrial effective refractory periods and increased inducibility of atrial fibrillation.<sup>6,7</sup> Very mobile ASAs in adults, and ASAs in children, were associated with atrial fibrillation. Atrial septal abnormalities (ASA, PFO, or both) favour local stretching of the atrial septum which could increase atrial vulnerability

**Abbreviations:** ASA, atrial septal aneurysm; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography



**Figure 1** Meta-analysis of case-control studies in patients with cryptogenic strokes. CI, confidence interval; OR, odds ratio.<sup>2</sup>

due to modifications of the electrophysiological substrate; the PFO could also create haemodynamic stretching of the atrial septum, particularly with the Valsalva manoeuvre.<sup>5</sup>

In practice, the lack of clues or of a smoking gun favouring one hypothesis or the other preclude making a definite conclusion regarding the causality of PFO or ASA in patients with a cryptogenic stroke. From a therapeutic point of view, we have to consider these abnormalities as risk factors rather than as an actual cause of stroke. Treating a risk factor is to aim at reducing the level of risk. Therefore, the next question is: what is the level of risk of a recurrent stroke in the presence of PFO, ASA or both?

### RISK OF RECURRENT STROKE IN THE PRESENCE OF PFO OR ASA

Only one prospective study is available, the FOP/ASA collaborative study, which included 592 patients with a cryptogenic stroke younger than 55 years. They all had a TOE to look for atrial septal abnormality. They were all treated with aspirin 300 mg/day and followed for four years.<sup>8</sup> In this study, it is possible that the patients considered at high risk were treated outside the registry by their neurologist or cardiologist, since we do not know the proportion of eligible patients seen during the study period who were actually included in the registry.

After four years, the patients with a PFO had an annual risk of recurrent brain infarction of 0.6% (1% after adjustment for risk factors). Those with only an ASA (without PFO) had an annual risk close to zero; those with no septal abnormality (neither PFO nor ASA) had an annual risk of 1%; and those with PFO and ASA had a risk of 4% per year (table 1).

Therefore, only patients with PFO + ASA seem to be at a high risk of recurrence, which in turn favours the hypothesis of thrombus formation within the conduit of the PFO rather than the paradoxical embolism hypothesis, as the most common mechanism.

PICSS (PFO in cryptogenic stroke study),<sup>9</sup> a substudy of WARSS (warfarin aspirin in recurrent stroke study), did not confirm the importance of the tandem PFO + ASA

abnormality for risk of recurrent stroke. WARSS was a double blinded secondary prevention trial which included 2206 patients with a non-cardioembolic stroke with random assignment to warfarin (mean international normalised ratio (INR) 1.8) or aspirin (300 mg/day). PICSS included 630 patients among 2206 (28%); all had TOE, and 34% had a PFO (36% large, 64% small); after two years of follow up, there was no difference between patients with PFO on aspirin or warfarin (mean INR 2.02) with a two year risk of 16% and 23.7%, respectively; the two year risk of recurrent brain infarction, transient ischaemic attack (TIA) or death of all causes was 14.5% in patients with PFO (18.5% in the case of small PFO and 9.5% in the case of large PFO) and 15.4% in patients without PFO; in cases of stroke of unknown cause (244 patients), the two year risk was 14.3% in patients with PFO and 12.7% in those without PFO. In the presence of both PFO + ASA, the two year risk was 15.9%, which apparently contradicts the main result of the FOP/ASA study. However, both studies are not comparable because of different end points—inclusion of TIAs in PICSS (which is a rather soft end point, like chest pain would be without information on creatine kinase elevation), and inclusion of all cause mortality in the primary end point, which increases the “noise” in this elderly population compared to the FOP/ASA study where patients were younger and had only non-fatal recurrent strokes. In PICSS, patients with PFO and stroke of unknown cause had fewer primary end points on warfarin (16.7%) than on aspirin (23.2%), a difference which was, however, not significant ( $p = 0.48$ ).

### WHAT ABOUT PFO IN ELDERLY PEOPLE?

A meta-analysis showed that the relation with stroke of unknown cause is much weaker in patients older than 60 years than in the young.<sup>2</sup> In fact, many additional potential causes and risk factors exist in these patients such as hypertension, diabetes, atherosclerosis of the aortic arch or of intracranial arteries involving medium sized arteries (not imaged by magnetic resonance angiography or even direct angiography), and lipohyalinosis (mostly hypertensive arteriopathy) involving arteries less than 300  $\mu$ m with normal angiography. Thus, the finding of a simple PFO on TOE is of uncertain relevance as cause/source of emboli in these

**Table 1** Risk of recurrent brain infarction according to presence or absence of PFO and ASA in a registry of patients with a cryptogenic stroke. Adapted from Mas *et al*<sup>8</sup>

	1 year (95% CI)	2 years (95% CI)	3 years (95% CI)	4 years (95% CI)	Mean annual risk
No PFO no ASA	2.0 (0.4 to 3.6)	3.7 (1.6 to 5.8)	4.2 (1.8 to 6.6)	4.2 (1.8 to 6.6)	1.1
PFO only	1.8 (0.05 to 3.6)	1.8 (0.05 to 3.6)	2.3 (0.3 to 4.3)	2.3 (0.3 to 4.3)	0.6
ASA only	0	0	0	0	0
PFO + ASA	2.0 (0 to 5.8)	4.0 (0 to 9.4)	6.3 (0 to 13.2)	15.2 (1.8 to 28.5)	4.0

ASA, atrial septal aneurysm; CI, confidence interval; PFO, patent foramen ovale.

patients. To close a PFO in these patients is simply to consider PFO as “guilty by association”, which, to me, is not good medicine.

### WHICH THERAPEUTIC STRATEGIES IN 2004?

Pending randomised controlled trials which are strongly needed, we recommend aspirin as first line treatment in patients with only a PFO or only an ASA, if there is no other additional factor, since their risk is 1%/year or less (level 2C recommendation). In case of an association of both PFO and ASA, or in case of a PFO associated with a hypercoagulable state, or with a history of unexplained brain infarction or TIA, or with a deep vein thrombosis preceding the stroke, data are insufficient to establish firm recommendations. A variety of therapeutic options exist, including long term antiplatelet treatment (monotherapy or combination therapy) or long term anticoagulation (at the expense of an annual risk of major bleeding of 2% per year), or percutaneous or surgical closure of the PFO. All these options will have to be properly tested in randomised controlled trials before they can be accepted in routine practice.<sup>10</sup>

In our centre, because of the 2.2% annual risk of bleeding on oral anticoagulant (0.2% fatal) found in the 150 patients of a consecutive series of 278 patients with a PFO, we propose percutaneous PFO closure, pending a randomised controlled trial in which we would like to randomise the patients.

In patients younger than 60 years with a cryptogenic brain infarction, our current indications for PFO closure are:

- PFO associated with ASA, because of the 4% annual risk on aspirin
- PFO associated with a clinical or magnetic resonance imaging history of unexplained stroke

- PFO associated with recurrent brain infarction or TIA while on antithrombotic treatment
- PFO associated with deep vein thrombosis before the stroke.

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