An endovascular device to close a patent foramen ovale

Patent foram

Jean-Louis Mas

Service de Neurologie, Hôpital
Sainte-Anne, 1 rue Cabanis, 75674
Paris Cedex 14, France; E-mail:
mas@chsa.broca.inserm.fr
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but does it prevent stroke?

foramen ovale and stroke

The foramen ovale is a natural interatrial channel, which normally closes soon after birth when pressure in the left atrium comes to exceed that in the right atrium. However, in about 30% of the population, the foramen stays patent throughout life, providing a potential channel through which blood may shunt from the right to the left atrium (Hagen *et al.* 1984). Over the past 15 years, several studies have shown that a patent foramen ovale (PFO) is detected more frequently in patients with an otherwise unexplained ischaemic stroke than in control subjects, or in patients with an identifiable cause of stroke (Lechat *et al.* 1988; Webster *et al.* 1988; Overell *et al.* 2000). However, the nature of the link between this common cardiac abnormality and stroke is unclear (Mas 1996). The difficulty in proving a causal relationship between PFO and stroke in the individual patient, and the lack of randomised trials, has left clinicians very uncertain how to prevent stroke recurrence. Moreover, the recent finding that PFO may not be a significant predictor of stroke recurrence in cryptogenic stroke patients contrasts with the increasingly numerous reports of transcatheter or surgical closure of the foramen (Devuyst *et al.* 1996; Homma *et al.* 1997; Hung *et al.* 2000; Windecker *et al.* 2000; Mas *et al.* 2001; Homma *et al.* 2002; Martin *et al.* 2002). All this has led to renewed debate about the best management of ischaemic stroke patients who are found to have a PFO.

PREVALENCE AND DIAGNOSIS

PFO is common in the general population. In an autopsy study of 965 normal hearts the prevalence was 27%, with no gender difference (Hagen *et al.* 1984). PFO was present in about 35% of people younger than 30 years and in about 25% of those older than 30. The maximum size of the foramen ranged from 1 to 19 mm, with a mean of 4.9 mm. A familial aggregation of PFO, particularly in women, has been reported (Arquiza *et al.* 2001).

PFO is frequently associated with an atrial septal aneurysm (ASA), a cardiac abnormality itself associated with stroke (Cabanès *et al.* 1993). In studies using transoesophageal echocardiography (TOE), about 20% of stroke patients with PFO also have an ASA, the prevalence of which increases with the degree of shunting (Lamy *et al.* 2002).

Transoesophageal echocardiography with injection of microbubble contrast agents into a cubital vein is more sensitive than the transthoracic approach and is currently the best method for the diagnosis of PFO. Examinations are performed at rest and during provocative manoeuvres to increase sensitivity (Valsalva and coughing). Passage of microbubbles into the left atrium within three cardiac cycles after opacification of the right atrium identifies a right-to-left shunt, which is due to a PFO in the majority of cases. The degree of shunting is usually graded as small, moderate or large by visual assessment of the number of microbubbles appearing in the left atrium. Inter- and intra-observer agreement for the assessment of degree of shunting is substantial but not perfect, with kappa values of 0.77 and 0.82, respectively. The best kappa statistics are obtained when no and small shunts were pooled and compared with larger shunts (Cabanès *et al.* 2002).

This semiquantitative grading of PFO shunting has been criticized because the shunting may vary with the haemodynamic and respiratory conditions, and the type and level of strain exerted during any provocative manoeuvres (Valsalva or coughing), and because the microbubble count is derived from a single 2D imaging plane. In addition, because superior vena caval flow is directed to the tricuspid valve and inferior vena caval flow to the right atrial septum, contrast injection into a cubital vein may be less sensitive than femoral contrast injection (Hamann *et al.* 1998).

Direct measurement of the maximum size of the foramen during TOE may be a more accurate means of assessing a PFO (Schuchlenz *et al.* 2002). However, the separation between the septum primum and septum secundum also varies with the haemodynamic and respiratory conditions. Moreover, because of the anatomy (i.e. the conduit is short and angled), it may be difficult to reliably measure the maximum size of the opening.

A number of studies have shown that contrast-enhanced transcranial Doppler examination of the middle cerebral artery to detect

arterial bubbles is highly sensitive and specific compared with contrast TOE to detect a right-to-left shunt (Droste *et al.* 1999). Although a negative contrast transcranial study may avoid the need for a TOE for the diagnosis of PFO, because transcranial Doppler does not provide any information about *other* potentially important cardiac embolic sources, TOE remains the investigation of choice in young patients with ischaemic stroke.

PATENT FORAMEN OVALE IS DETECTED MORE FREQUENTLY THAN EXPECTED IN YOUNG ADULTS WITH CRYPTOGENIC STROKE

There are many case-control studies examining the frequency of PFO in patients with stroke or transient ischaemic attack (TIA) in comparison with control subjects, or patients with a known cause of stroke. In a systematic review of these case-control studies, widely different detection rates of PFO were observed, ranging from 10% to 44% for stroke, 31% to 77% for cryptogenic stroke, 4% to 25% for known stroke cause, and 3% to 22% for control subjects (Overell *et al.* 2000). Such variation arises from interobserver variability in the diagnosis of these septal abnormalities, different diagnostic techniques and the criteria employed, and methodological inconsistencies (Overell *et al.* 2000; Cabanès *et al.* 2002). In studies comparing patients with ischaemic stroke with non-stroke control subjects, PFO was significantly associated with stroke in some but not all studies, giving a combined odds ratio of 1.8 (95% CI 1.2 to 2.7). There was significant heterogeneity, largely as a result of the different ages of the participants. PFO was significantly associated with ischaemic stroke in patients younger than 55 years (odds ratio 3.1, 95% CI 2.3 to 4.2), but not in those older than 55 (odds ratio 1.3, 95% CI 0.8 to 2.0). A similar pattern was observed when patients with cryptogenic stroke were compared with non-stroke control subjects, or with patients with a known stroke cause. It should be stressed however, that less work has been conducted in the older age group where a true association may be difficult to detect because other stroke causes and risk factors are more likely to play their part.

As PFO is common in patients without stroke, it is clinically useful to characterize PFO into those more likely or less likely to be associated with stroke. In this respect, several investigators have suggested that patients who have an ASA in

addition to PFO may have a higher risk of stroke (Cabanès *et al.* 1993; Overell *et al.* 2000). Several studies have also suggested that a more severe right-to-left shunt, a larger opening of the PFO, and right-to-left shunting at rest (as opposed to only during provocative manoeuvres) may reflect a particularly high stroke risk (Hausmann *et al.* 1995; Serena *et al.* 1998; De Castro *et al.* 2000; Schuchlenz *et al.* 2000). Most of these studies, however, did not focus on the association of PFO with ASA, so the associations may partly be with both lesions together rather than with PFO alone, given the increasing prevalence of ASA with the degree of shunting.

IS THERE A CAUSAL LINK BETWEEN PFO AND STROKE?

Statistical association, as demonstrated by case-control studies, does not necessarily reflect cause and effect. Such association may also result from bias, chance or confounding. Selection, or information, bias and chance are unlikely to explain the findings of the numerous independent studies linking PFO to stroke. However, it is more difficult to exclude an indirect association, i.e. the presence of an as-yet unknown confounding factor, which could be associated with PFO as well as with stroke. The relevance of PFO in the aetiology of ischaemic stroke will only be confirmed when randomised controlled trials demonstrate that 'removal' of this septal disorder, by endovascular or surgical techniques, substantially reduces the risk of subsequent stroke; in the same way that the relevance of carotid stenosis was confirmed by the finding that carotid endarterectomy substantially reduces the risk of ipsilateral ischaemic stroke.

WHAT ARE THE POTENTIAL MECHANISM(S) FOR ANY PFO-ASSOCIATED STROKE?

The mechanism of stroke in patients with a PFO is still unclear. Many think that stroke results from paradoxical embolism of thrombotic material from the venous bed into the arterial circulation. Direct evidence for this comes from case reports in which a thrombus was visualized within a PFO, but such cases are very unusual (Mas 1996) (Fig. 1).

Documentation of a venous source of embolism and/or pulmonary embolism is a key criterion for the diagnosis of paradoxical embolism, but this criterion is neither specific nor sensitive. The occurrence of stroke in a patient with recently diagnosed venous thrombosis, or

Figure 1 This post mortem specimen shows a (a) venous thrombosis (arrow) passing through a defect in the interatrial septum, and (b) another part of the same thrombosis (arrow) in the carotid artery in the neck. This is a most unusual specimen, either because this mechanism of stroke is rare, or because the chances of a thrombosis being 'caught' at exactly the right moment are very low. Clearly paradoxical embolism can and does occur, but how often does it actually cause stroke?

simultaneous pulmonary and systemic embolism, strongly suggests paradoxical embolism, but these situations are rare. Just demonstrating venous thrombosis does not mean that paradoxical embolism has occurred (or will occur again), because venous thrombosis in a stroke patient may just be a consequence of immobilization due to the stroke rather than the cause of stroke. In most patients with PFO-associated stroke, venous thromboembolism cannot be demon-

strated (Ranoux *et al.* 1993; Lamy *et al.* 2002). Of course, failure to document a venous source of embolism may mean not just that paradoxical embolism has not occurred, but also maybe that any venous thrombi have simply not been detected because of their location or small size. Furthermore, venous thrombi may disappear either spontaneously or after anticoagulation, before investigations are performed. Thus, failure to document venous thrombi does not exclude paradoxical embolism in a PFO patient.

Other potential mechanisms of stroke include direct embolization of thrombi formed locally within the PFO, or an associated ASA (Silver & Dorsey 1978; Schneider *et al.* 1990), and the formation of intracardiac thrombus as a result of atrial arrhythmias (Berthet *et al.* 2000), but documentation of these mechanisms has been unrewarding (Lamy *et al.* 2002).

Thus, in most cases of cryptogenic ischaemic stroke with PFO, there is no direct evidence of paradoxical embolism, intracardiac thrombosis, or arrhythmias. This suggests that other mechanisms are operating in many cases, perhaps in the majority. Nonetheless, it should be kept in mind that PFO is a common finding in the normal population and must coexist by chance alone in one-third of young adults with ischaemic stroke. Consequently, there are inevitably patients in whom stroke is erroneously attributed to a PFO.

WHAT IS THE RISK OF STROKE RECURRENCE?

There are not many studies of the risk of stroke recurrence in patients with PFO. Only those that included more than 100 unselected patients will be reviewed (Table 1). In our first study 132 patients less than 60 years of age with PFO, ASA, or both and an otherwise unexplained stroke or TIA were identified in 11 neurological centres (Mas & Zuber 1995). Most of these patients received antiplatelet drugs for secondary prevention. Only two strokes and four TIAs occurred, the risk of a

recurrent stroke at 2 years was 2.3% (95% CI 0.6% to 8.2%), while the risk of having a stroke or a TIA was 6.7% (95% CI 3.1% to 14.2%). The association of ASA and PFO was an indicator of a higher risk of recurrent events.

Bogousslavsky and colleagues reported on 140 patients aged 60 years or less with an ischaemic stroke or a TIA and a PFO, admitted to a population-based primary-care centre (Bogousslavsky *et al.* 1996). During a mean follow-up of 3 years, eight strokes, eight isolated TIAs and five deaths occurred in patients treated with aspirin, warfarin or surgery. The presence of an atrial septal defect, a coexisting alternative cause of stroke, a history of recent migraine, and infarction in the posterior cerebral artery territory were all associated with recurrence, whereas the presence of an ASA and type of treatment were not.

In Nedeltchev and colleagues' study, seven strokes and 14 TIAs occurred in 157 patients with stroke or TIA and a PFO, who received antiplatelet drugs or oral anticoagulants for secondary prevention (Nedeltchev *et al.* 2002). The cumulative risk of recurrent stroke was 4.5% (95% CI 2.5% to 6.5%) at 2 years and that of recurrent stroke or TIA was 9.2% (95% CI 6.5% to 11.9%). Patients with multiple cerebrovascular events before the diagnosis of the PFO had a higher rate of recurrent stroke than those with a first ever stroke or TIA. Neither the severity of the right-to-left shunt, nor the coexistence of an ASA in addition to the PFO were associated with an increased risk of stroke recurrence.

These three retrospective studies indicate that the overall risk of stroke recurrence in predominantly young patients with a PFO and an otherwise unexplained ischaemic stroke or TIA is about 1–2% per year, at least for the first 2 or 3 years. Confidence intervals however, are wide and treatments were not standardized. In addition, none of these studies included a control group of patients with no septal abnormalities, precluding any conclusion on the role of PFO as a significant predictor of stroke recurrence in cryptogenic stroke patients.

Table 1 Average annual rates of recurrent cerebrovascular events in patients with PFO

Study	Prospective?	Standardised treatment?	Control group?	Number of patients	Mean age	Follow-up (months)	Stroke recurrence*	Stroke + TIA recurrence*
Mas <i>et al.</i> (1995)*	No	No	No	132	40	22	1.2%/ year	3.4%/ year
Bogousslavsky <i>et al.</i> (1996)	No	No	No	140	44	36	1.9%/ year	3.8%/ year
Nedeltchev <i>et al.</i> (2002)*	No	No	No	159	51	29	1.8%/ year	5.5%/ year
PFO-ASA study (2001)*	Yes	Yes	Yes	267/314	40	38	1.3%/ year	2. 2%/ year

*Average annual rates were calculated from the published cumulative risk of recurrence.

In our Patent Foramen Ovale and Atrial Septal Aneurysm (PFO-ASA) study we used a standard treatment (aspirin, 300 mg a day) and assessed *prospectively* the absolute and relative risks of recurrent cerebrovascular events associated with PFO, ASA, or both (Mas *et al.* 2001). In 581 consecutive patients aged between 18 and 55 years with a recent ischaemic stroke of unknown origin, TOE was performed according to a standard protocol and two sonographers who were unaware of patient clinical data and outcome reviewed all the videotapes independently. Of the 581 patients, 304 had no septal abnormality, 216 had an isolated PFO, 10 an isolated ASA, and 51 had both PFO and ASA. During a mean follow-up of about 3 years, 24 patients had a stroke and 13 additional patients had a TIA. At 4 years, the risk of recurrent stroke was 2.3% (95% CI 0.3% to 4.3%) in patients with isolated PFO, 15.2% (95% CI 1.8% to 28.6%) in those with both PFO and ASA, and 4.2% (95% CI 1.8% to 6.6%) in those with none of these cardiac abnormalities. No recurrence occurred in patients with isolated ASA. The corresponding average annual rates of recurrent stroke were 1.1% in patients with no septal disorder, 0.6% in those with isolated PFO, and 4% in those with both PFO and ASA. The average annual rates of recurrent stroke or TIA were, respectively, 1.6%, 1.4%, and 5.2%. The presence of *both* cardiac abnormalities was the only septal disorder significantly associated with an increased risk of recurrent stroke (Fig. 2). Patients with both PFO and ASA had a risk of recurrent stroke four times higher than patients with no septal abnormality (hazard ratio, 4.2; 95% CI: 1.5 to 11.8). The presence of an isolated PFO, whether small or large, was not a significant predictor of recurrent cerebrovascular events.

The Patent foramen ovale In Cryptogenic Stroke Study (PICSS; Homma *et al.* 2002) was part of the Warfarin Aspirin Recurrent Stroke Study (WARSS; Mohr *et al.* 2001), a double blind trial that randomised 2206 stroke patients to either warfarin (to achieve and maintain an INR 1.4–2.8) or aspirin (325 mg a day) and was followed for 24 months. Cryptogenic stroke patients were asked to undergo TOE. PICSS also included all WARSS patients who underwent TOE for clinical purposes. Of the 601 stroke patients (mean age 59 years) enrolled in PICSS, 250 had had a cryptogenic stroke and 203 had a PFO (33.7%). There was no significant difference in the time to stroke or death between those with and those without PFO in the overall population, or in the cryptogenic subset

(Table 2). Nor was there any significant difference between those with no, small, and large PFO. Patients with PFO alone and those with PFO and ASA experienced similar 2-year event rates (14.5% vs. 15.9%). The difference between these findings and the PFO-ASA study may be a result of several factors – older patients, non-cryptogenic as well as cryptogenic strokes, and using death as well as stroke as the outcome of interest. Although in stroke patients with and without PFO, therapy with warfarin or aspirin resulted in similar rates of adverse events, among the cryptogenic subgroup, in patients with and without PFO, there was a trend toward primary event reduction in the warfarin-treated patients (Table 2). The risk of major haemorrhage was similar in the patients receiving warfarin and those receiving aspirin, but the rate of minor haemorrhage was significantly higher in the warfarin group.

Figure 2 PFO-ASA study: probability that patients will remain free from recurrent stroke or transient ischaemic attack, according to the presence or absence of atrial septal abnormalities (Mas *et al.* 2001). The numbers at the bottom refer to the patients still at risk of stroke/TIA at various points in time. PFO, patent foramen ovale; ASA, atrial-septal aneurysm.

Table 2 Two-year rates of recurrent stroke or death in the PICS study*

	With PFO	Without PFO	Hazard Ratio (95% CI)
Entire PICSS cohort (N = 601)	203 (14.8%)	398 (15.4%)	0.96 (0.62–1.48)
Warfarin	97 (16.5%)	195 (13.4%)	
Aspirin	106 (13.2%)	203 (17.4%)	
Cryptogenic cohort (N = 250)	98 (14.3%)	152 (12.7%)	1.17 (0.60–2.37)
Warfarin	42 (9.5%)	72 (8.3%)	
Aspirin	56 (17.9%)	80 (16.3%)	

*From Homma *et al.* 2002.

WHAT IS THE BEST TREATMENT FOR SECONDARY PREVENTION?

Secondary prevention for stroke patients with PFO and/or ASA is the subject of very considerable debate. Therapeutic options include antiplatelet drugs, oral anticoagulants, transcatheter closure of the foramen and open-heart surgery. However, there are no published data showing convincingly the superiority of any one of these strategies.

Antiplatelet drugs are well tolerated and reduce recurrent ischaemic events when used for secondary prevention in the generality of ischaemic stroke survivors and TIA patients. There is no reliable information for PFO patients. They may in theory be useful if abnormalities of the endocardial surface of the interatrial septum are a nidus for activation of platelets.

Chronic anticoagulation may be more useful than antiplatelet drugs if stasis-related thrombi originate in the cardiac chambers or the peripheral venous system. But the potential benefit of anticoagulation is counterbalanced by the increased risk of major bleeding (Hart *et al.* 1995). Although younger patients are at lower risk for anticoagulation complications, they are exposed to the hazard for longer.

Closure of the foramen ovale by surgical (Devuyst *et al.* 1996; Homma *et al.* 1997) or transcatheter (Hung *et al.* 2000; Windecker *et al.* 2000; Martin *et al.* 2002) techniques can prevent paradoxical embolism, but this will not be relevant if a PFO-unrelated mechanism of ischaemic stroke is the cause. Anyway, if paradoxical embolism is indeed the actual mechanism of recurrent stroke in PFO patients, PFO closure will only prevent arterial embolism, not venous thromboembolism with its potentially serious consequences such as pulmonary embolism.

Transcatheter closure of PFO is less invasive than open-heart surgery but is not without risks. These include complications related to vascular access, cardiac perforation with and without

tamponade, air embolism, device embolization, arrhythmias and intracardiac thrombus formation, some of which may be responsible for periprocedural stroke (Hung *et al.* 2000; Windecker *et al.* 2000; Martin *et al.* 2002). The long-term risks and benefits of PFO closure are not known. In uncontrolled studies, the average annual rates of recurrent thromboembolic events were comparable to previously published data on medical treatment of PFO (Hung *et al.* 2000; Windecker *et al.* 2000; Martin *et al.* 2002).

Pending data from properly designed randomised trials (see below), our current strategy for secondary prevention is based on the results of the PFO-ASA and PICS studies. Both concluded that when patients are treated with aspirin, the presence of a PFO, whether small or large, does not increase the risk of recurrent stroke. In addition, in the PFO-ASA study, young patients (18–55 years of age) with isolated PFO had a low risk of stroke recurrence on aspirin. Therefore, we favour aspirin as an initial therapy for secondary prevention in patients with an isolated PFO and a first otherwise unexplained ischaemic stroke. If there is good evidence for concomitant venous thrombosis and/or pulmonary embolism, anticoagulant therapy is given as long as the risk of venous thromboembolism is thought to persist. Long-term anticoagulation or PFO closure may be indicated in patients with a high risk of recurrent venous thromboembolism, or with recurrent cerebral ischaemia on antiplatelet drugs.

According to the PFO-ASA study, young cryptogenic stroke patients who have an ASA in addition to a PFO have a high risk of stroke recurrence on aspirin. Whether these patients would benefit from more aggressive therapeutic strategies, such as oral anticoagulants or correction of the cardiac abnormalities, remains to be assessed in randomised trials. Pending further information, we favour oral anticoagulants as the initial therapy in this subgroup of patients, mainly on the basis of their efficacy against thrombus formation and embolism across a wide range of thrombogenic mechanisms. Transcatheter PFO closure is our final option, when recurrent strokes occur despite optimal antithrombotic therapy.

In the rare case of an impending paradoxical embolism discovered at echocardiography, intracardiac embolectomy with correction of the intracardiac defect has been the preferred treatment. Thrombolytic therapy or anticoagulation with intravenous heparin may help if emergency surgery is not feasible (Mas 1996).

Clearly, all the therapeutic options have risks and unless randomised trials can define who should be treated with what (if anything), and for how long, we could end up exposing patients to unnecessary complications of treatment.

If you wish to join a trial of PFO closure then E-mail: the author of this article to get details of his planned trial, or contact the trial being conducted by Heinrich Mattle in Switzerland (http://www.drabo.de/dL/pctrial_ch.pdf).

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