Absence of recurrent stroke after percutaneous closure of patent foramen ovale despite residual right-to-left cardiac shunt assessed by transcranial Doppler

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Summary
Background. — Percutaneous transcatheter closure of patent foramen ovale has been proposed to prevent recurrent strokes in young adults. Contrast transcranial Doppler ultrasonography provides a functional, semiquantitative evaluation of right-to-left cardiac shunt.
Aims. — To evaluate the efficacy of percutaneous closure of patent foramen ovale in suppressing right-to-left shunt (assessed using transcranial Doppler) and in preventing secondary stroke.

Abbreviations: ASA, Atrial septum aneurysm; ASD, Atrial septal defect; CT, Computed tomography; ECG, Electrocardiogram; IVC, Inferior vena cava; MES, Microembolic signals; MRI, Magnetic resonance imaging; PFO, Patent foramen ovale; R/L, Right-to-left; TCD, Transcranial Doppler; TEE, Transesophageal echocardiography; TIA, Transient ischaemic attack; TTE, Transthoracic echocardiography.

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Methods. — Sixty-six patients less than 55 years of age were selected from 81 consecutive patients evaluated for percutaneous closure of patent foramen ovale after one or more cryptogenic stroke. All patients presented with a right-to-left cardiac shunt and passage of more than 50 microbubbles or curtain pattern on transcranial Doppler. Follow-up tests included cardiac and neurological clinical evaluation, contrast transcranial Doppler, and echocardiography.

Results. — Percutaneous closure was successful in all patients, without major persistent side-effects. Before closure, the rate of recurrent stroke events was 16.57 per 100 patient-years; after closure, no recurrent stroke events (including transient ischaemic attacks) occurred during a mean follow-up period of 3.73 years (p = 0.0001). Contrast transcranial Doppler detected residual right-to-left cardiac shunt in 25/60 (41.7%) patients evaluated after 12 months; 20.0% of these patients had passage of more than 50 microbubbles on transcranial Doppler.

Conclusion. — Contrast transcranial Doppler is a useful tool in the selection of patients for percutaneous closure of patent foramen ovale. The absence of recurrent stroke events after transcatheter closure suggests that this procedure may prevent stroke by changing the foramen ovale configuration, even in cases of persisting shunt. Larger studies are needed to confirm these data.

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Résumé

Historique. — La fermeture percutanée du foramen ovale perméable est proposée pour prévenir la récidive d’accident vasculaire cérébral chez le jeune adulte. Le doppler transcrânien réalisé avec injection de contraste permet une évaluation semi-quantitative du shunt cardiaque droit–gauche.

Objectif. — Le but de l’étude est d’évaluer l’efficacité de la fermeture percutanée du foramen ovale perméable dans la prévention secondaire de l’accident vasculaire cérébral et dans la disparition du shunt droit–gauche mis en évidence par doppler transcrânien.

Méthodologie. — Soixante-six patients âgés de moins de 55 ans et ayant présenté au moins un accident vasculaire cérébral cryptogénique ont été retenus parmi 81 patients adressés consécutivement pour fermeture percutanée d’un foramen ovale perméable. Tous présentaient un shunt cardiaque droit–gauche avec passage de contraste au doppler transcrânien de plus de 50 microbulles au sein du “rideau”. Le suivi clinique cardiologique et neurologique fut associé à un suivi par doppler transcrânien et par échocardiographie.

Résultats. — Avant fermeture, le taux de récidive d’accident vasculaire cérébral était de 16,57 par 100 années-patients. La fermeture fut réalisée avec succès chez tous sans effets secondaires majeurs persistants. Aucune récidive d’accident ischémique transitoire, ni d’accident vasculaire cérébral ne survint pendant un suivi moyen de 3,73 ans (p = 0,0001). Les contrôles par doppler transcrânien ont détecté une incidence de 41,7 % de shunts cardiaques droite–gauche résiduels après une année parmi lesquels 20 % avec passage de plus de 50 microbulles.

Conclusions. — Le doppler transcrânien réalisé avec injection de contraste est utile pour sélectionner les patients avant fermeture percutanée d’un foramen ovale perméable. L’absence de récidive d’accident vasculaire cérébral malgré la persistance d’un shunt résiduel suggère que la fermeture percutanée pourrait prévenir les récidives d’accident vasculaire en modifiant la configuration du foramen ovale. Des études complémentaires sont nécessaires pour confirmer cette hypothèse.

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Introduction

Recent studies have shown that patent foramen ovale (PFO) is associated significantly with cryptogenic stroke in the young patient [1]. A wide opening of the PFO [2] and its association with atrial septal aneurysm (ASA) [3] have been identified as indicators of a particularly high stroke risk. Transesophageal echocardiography (TEE) with contrast injection is considered to be the investigation of choice for detecting right-to-left (R/L) shunt associated with PFO, and for excluding other cardioembolic causes of stroke. However, estimation of the PFO size by TEE remains difficult [4]. Contrast transcranial Doppler (TCD) ultrasonography is an alternative method for detecting R/L shunts [5,6] and provides a semiquantitative evaluation of the R/L shunt in the brain [7]. Percutaneous PFO closure has been proposed as an alternative strategy to surgery or long-term anticoagulation in the prevention of recurrent stroke [8]. We conducted a prospective study of the percutaneous closure of PFO in patients whose shunt was discovered after one or more cryptogenic stroke. The purpose of the study was to assess the efficacy of percutaneous PFO closure in preventing sec-
ondary stroke events (including transient ischaemic attack (TIA)) by the correction of significant R/L shunting.

**Patients and methods**

**Patients**

Eligible patients had experienced one or more cryptogenic stroke. Diagnosis of cryptogenic stroke was based on unequivocal acute focal neurological deficit due to a cerebral ischaemic lesion, demonstrated by computed tomography (CT) scan and/or cerebral magnetic resonance imaging (MRI), with the exclusion of all possible causes other than a PFO.

Normal results were required for the following examinations:
- cerebral MRI, except for the ischaemic lesions;
- angio-MRI of the circle of Willis, and — in selected doubtful cases — cerebral angiography;
- continuous wave Doppler and color duplex echography of extracranial cervical arteries;
- 12-lead electrocardiogram (ECG);
- 24h electrocardiographic Holter monitoring;
- TEE, except for the presence of PFO with or without ASA;
- standard TCD ultrasonography.

Routine blood tests and an extensive work-up were carried out to exclude hypercoagulable status (i.e. antithrombin deficiency, protein C or S deficiency, antiphospholipid antibody syndrome, hyperhomocysteinaemia, activated protein C resistance, factor V Leiden mutation, prothrombin G20210A gene mutation).

**Echocardiography**

PFO was demonstrated by transthoracic echocardiography (TTE) and/or TEE with R/L interatrial shunting of contrast at rest and/or during a Valsalva manoeuvre. Contrast medium consisted of 1 mL air mixed with 9 mL saline solution, and was injected rapidly into an antecubital vein via a 20 gauge catheter. Passage of a significant number of microbubbles on TEE during three cardiac cycles [9] was required if a patient was to be considered for PFO closure. ASA was defined as abnormally redundant interatrial septum with an excursion greater than or equal to 10 mm [4] into the right atrium or the left atrium, and was noted but not required.

**Transcranial Doppler microembolic signal detection**

TCD ultrasonography detection of microembolic signals (MES) was performed using a Multidop X-4 TCD 8 (DWL°) monitoring device. The middle cerebral arteries were monitored simultaneously through the temporal window using multigate 2 MHz probes. TCD probes were fitted to a light metal frame, which was fixed firmly to the head by two earpieces and an adjustable nose saddle (manufactured by DWL). A scale between −50 and +150 cm/s with an 8 mm axial length of the sample volume, a 128-point fast Fourier transform resolution, and detection thresholds of 9 dB above the Doppler background were used to identify MES and a temporal delay between the different samples on each probe. Data from both channels were recorded onto a hard disk. All patients had appropriate echo windows with adequate echo signals.

The contrast medium used was the same as that used for TEE, consisting of agitated saline. During the test, with the patient lying comfortably in the supine position, 10 mL of contrast medium were injected into a large antecubital vein via a 20 gauge catheter (twice at rest, three times with a Valsalva manoeuvre for 5–10 s starting 5 s after the start of the injection, and once while coughing). The following definition of MES was used: typical, visible and audible, short-duration, high-intensity signal within the Doppler flow spectrum, with a time delay in the two channels within each side [10]. Two experienced observers counted the separate MES on the two sides during offline analysis. An uncountable signal pattern caused by a high number of MES during a very short period was called a curtain pattern, as described previously [11]. Shunts were categorized as followed:
- less than 10 MES, no or trivial shunt;
- 10–50 MES, moderate shunt;
- more than 50 MES or curtain pattern, large shunt.

Passage of more than 50 microbubbles or a curtain pattern appearing once during the procedure was required for percutaneous PFO closure.

**PFO closure**

Venous access was obtained through the femoral vein, under general anaesthesia. PFO and occluder size were determined from the TEE evaluation, and the maximum PFO dimension was determined by measuring the balloon-stretched diameter. Four different devices (Helex 1; Amplatzer PFO occluder 5; PFO Star/Cardia Star 48; Cardioseal/Starflex 12) were implanted under fluoroscopic guidance with TEE monitoring. Patients were treated with aspirin 160 mg once daily for six months to provide antithrombotic protection until full device endothelialization. Patients with a PFO Star closure received clopidogrel 75 mg once daily for six weeks after device implementation. Treatment was withdrawn after six months. Prophylaxis against Osler’s endocarditis was also recommended for the first six months after closure.

**Follow-up**

After PFO closure, patients were followed by a neurologist and a cardiologist for clinical outcome and side effects. The primary endpoint was recurrent stroke event, including TIA or peripheral emboli; the secondary endpoint was persistence of a significant residual R/L shunt on contrast TCD ultrasonography. Clinical, TTE, and contrast TCD ultrasonography evaluations were carried out at three, six, and 12 months. In cases of significant persisting shunt, TEE was performed at 12 months. Recurrent stroke event rates were calculated as the ratio of the total number of recurrent stroke events to the total number of follow-up years since the first stroke event, divided by 100 to yield recurrent stroke event rates per 100 patient-years [8].
Statistical analysis
Continuous variables were compared using a Wilcoxon test, as variables did not present a normal distribution. Proportions were compared using Fisher’s exact test. The numbers of ischaemic events before and after treatment were compared using the median test. A p-value of 0.05 was considered to be significant. We used SAS version 8.0 statistical software (SAS Institute Inc., Cary, NC, USA).

Results
Patient characteristics
Between January 2000 and May 2005, 81 patients below 55 years of age (45 men and 36 women) were referred consecutively to undergo percutaneous transcatheter closure of PFO. Fifteen of these patients were excluded from the procedure for the following reasons:
- TIA only with no MRI lesion (n = 8);
- coexisting cervical arterial dissection (n = 1);
- hyperhomocysteinaemia related to the homozygote C677T MTHFR gene mutation (n = 1; this patient is receiving treatment to normalize the homocysteinaemia);
- hypercoagulable status related to factor V Leiden and prothrombin G20210A gene mutation (n = 2);
- moderate R/L shunt with 50 microbubbles or less, on contrast TCD ultrasonography (n = 3). One of the three patients with a moderate R/L shunt (45 microbubbles on TCD) had a new stroke during the study period; the others remain asymptomatic.

Percutaneous transcatheter closure of PFO was performed in 66 patients who fulfilled all the criteria for the procedure, and from whom written informed consent had been obtained. Patient characteristics are summarized in Table 1.

Nineteen (28.8%) patients had experienced more than one stroke events before PFO closure (mean 2.6 recurrent strokes; Table 1; Fig. 1) despite antithrombotic therapy that included at least aspirin (n = 14) and oral anticoagulation (n = 1). The mean observation period between the first and last stroke before PFO closure was 6.2 years (median: four years) in these patients. Seven of these patients had one or more recurrent stroke event in the year after the first stroke.

The median delay between first stroke and PFO closure was significantly longer in patients who had experienced a recurrent stroke event before PFO closure (4.3 years; range: three months to 22 years) than in patients who had experienced only one stroke before PFO closure (seven months; range: three months to seven years; p = 0.0001).

PFO closure
PFO size was measured with a balloon in the first 22 (33.3%) patients, but the procedure was not performed thereafter. The mean balloon-stretched dimension was 11 mm (median: 10.5 mm; range: 7–16 mm).

### Table 1 Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients, n</th>
<th>Mean age (median), years</th>
<th>Women, n (%)</th>
<th>Smoker, n (%)</th>
<th>Controlled arterial hypertension, n (%)</th>
<th>Controlled hyperlipaemia, n (%)</th>
<th>Scuba diver, n (%)</th>
<th>Atrial septal aneurysm, n (%)</th>
<th>Frequency of stroke events before PFO closure, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n</td>
<td>66</td>
<td>41.5 (43)</td>
<td>31 (47.0)</td>
<td>15 (22.7)</td>
<td>4 (6.1)</td>
<td>11 (16.7)</td>
<td>4 (6.1)</td>
<td>34 (51.5%)</td>
<td>47 (71.2)</td>
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<td>Mean age (median), years</td>
<td>2.74 (0.83)</td>
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<td>Women, n (%)</td>
<td>42 (64)</td>
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<td>8 (12.1)</td>
<td>10 (15.2)</td>
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<td>Smoker, n (%)</td>
<td>21 (31.8)</td>
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<td>3 (4.6)</td>
<td>7 (10.6)</td>
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<td>Controlled arterial hypertension, n (%)</td>
<td>6 (9.1)</td>
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<td>Controlled hyperlipaemia, n (%)</td>
<td>8 (12.1)</td>
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<td>Scuba diver, n (%)</td>
<td>3 (4.6)</td>
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<td>Atrial septal aneurysm, n (%)</td>
<td>24 (36.3)</td>
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<td>Frequency of stroke events before PFO closure, n (%)</td>
<td>30</td>
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<tr>
<td>Number of recurrent stroke events before PFO closure</td>
<td>6.57</td>
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<tr>
<td>Number of recurrent stroke events per 100 patient-years before PFO closure</td>
<td>2.74 (0.83)</td>
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<tr>
<td>Mean delay between first stroke event and PFO closure (median), years</td>
<td>3.73 (3.55)</td>
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An ASA was present in 34 patients (51.5%); the frequency of stroke was not significantly higher in patients with an ASA than in patients with PFO alone.

Percutaneous PFO closure was successful in all 66 patients. One patient had an iliac thrombosis and pulmonary embolism 27 days after the procedure, probably due to venous catheterization, and an asymptomatic intracardial thrombus on the PFO device was found in another patient at the three-month follow-up consultation; both of these patients were treated successfully with warfarin. One patient had a femoral arteriovenous fistula that resolved spontaneously. Two patients presented with an episode of acute atrial fibrillation a few days after device placement; these resolved quickly with medication.

Neurological follow-up
Follow-up data were available from 65 patients; one patient was lost to follow-up after moving back to the USA. During the follow-up period (mean: 3.73 years, median: 3.5, range: 1.36–6.75, total: 246 patient-years), no patient experienced a recurrent stroke or TIA, compared with 30 recurrent stroke events during the time from the first stroke event until PFO closure (mean: 2.74 years, median: 0.83, range: 0.22–22, total: 181 patient-years; p < 0.0001).

Persisting residual shunt
A residual shunt of more than 10 microbubbles at TCD ultrasonography assessment was present in 29/57 (50.9%)
patients evaluated three months after PFO closure, in 23/54 (42.6%) patients evaluated six months after PFO closure and in 25/60 (41.7%) patients evaluated 12 months after PFO closure; a persisting shunt of more than 50 microbubbles was present in 12 (20.0%) of these patients.

The presence of a residual R/L shunt on TCD did not correlate with the type of device used. The ratio of residual shunt to device used was 1:1 with Helex, 2:5 with AMPLATZER PFO occluder (40.0%), 23:48 with PFO Star/Cardia Star (47.9%), and 3:12 with Cardioseal/Starflex (25.0%).

TEE evaluation was carried out in 14/25 patients with residual significant shunt, and in 10/12 patients with a persisting shunt of more than 50 microbubbles at the 12-month follow-up TCD evaluation. In nine patients, the residual shunt was related to the device (protrusion of one left arm of the occluder into the right atrium, n = 1; persistent shunt through the device and/or abnormal mobility of the right disk and incomplete occlusion, n = 8).

In four patients, persisting shunts were associated with the presence of an additional atrial septal defect (ASD): three patients had a small additional ASD (a second device was implanted successfully in one of these patients, with complete suppression of the residual shunt; a second attempt at closure was not judged to be necessary for the other two patients, who had tiny ASDs located close to the aorta) and one patient presented with a neo-ASD created by the motion of a 38 Starflex device closing an aneurysmal PFO (this was closed successfully using an 8 mm Amplatzer). In one patient, no residual interatrial shunt was present, but an intrapulmonary shunt with bubbles coming from the upper right pulmonary was seen at contrast echo.

Discussion

We limited the indication for percutaneous PFO closure to patients below 55 years of age, with cryptogenic stroke and PFO associated with a significant R/L shunt (> 50 microbubbles or curtain pattern on contrast TCD). Only stroke events proved by CT scan or MRI and reported in detail by a neurologist were considered.

The balloon-stretched dimensions of the PFOs that were measured were large (7–16 mm), which indicates that a relevant shunt described by contrast TEE and TCD is associated with large PFO. There was a 51.5% incidence of ASA in our selected population, confirming the impression that ASA is associated with larger PFOs [3]. Our study illustrates the
potential benefits of contrast TCD for detection, functional evaluation of the shunt [12], and postprocedure control [13]. Before closure, 30 recurrent stroke events were observed during the 181 years of follow-up time from the first stroke event to PFO closure (16.57 stroke events per 100 patient-years) compared with no recurrent stroke events (including TIA) after closure during a total of 246 years of follow-up (p < 0.0001). Of the 19 patients who had a recurrent stroke event before PFO closure, seven had a new stroke in the year after the first event. In our study, the observation period before PFO closure was significantly longer (median 4.3 years) in patients who had a recurrent stroke event before PFO closure than in patients who only had one stroke before PFO closure (median: seven months; p = 0.0001). Patients who only had one stroke before PFO closure may have been selected for device closure earlier, preventing the recurrence of a neurological event.

Our results suggest that percutaneous PFO closure is useful in preventing secondary stroke in young patients presenting with large PFOs, and introduce reservations about the benefits of medical treatment in this population.

The high percentage (41.7%) of persisting shunts after PFO closure raises many questions and emphasizes the need for critical evaluation of the results of PFO closure. On TEE examination, residual shunts were related either to the device (incorrect device positioning or device not watertight) or to an additional ASD not covered by the device. None of the ASDs were seen on TEE before the percutaneous procedure, suggesting that PFO closure was necessary to allow a shunt through that small interatrial communication.

The high percentage of persisting shunts, and the complete absence of recurrent stroke events (including TIA) in this young, carefully selected population with cryptogenic stroke, seem to be contradictory findings. This inconsistency has led us to reconsider the goal of percutaneous PFO closure: whether it should be to abolish R/L shunt or to prevent the recurrence of stroke (the real endpoint)? Modifying the configuration of the interatrial septum by device placement may explain the lack of recurrent stroke or TIA despite the presence of a residual shunt. Anatomically, PFO is a funnel of varying length bounded by the septum secundum and septum primum. The PFO has an asymmetric configuration, with a larger orifice on the right side than on the left side (Fig. 2).

PFO function during fetal life is to direct the inferior vena cava (IVC) flow to the left atrium, allowing the blood oxygenated by the placenta to be directed preferentially to the brain. PFO anatomy is modified with PFO device placement [14]; both septa became coplanar and the PFO is no longer a funnel. Thanks to this new anatomy, clots could be less likely allowed to cross the persisting shunt from the right circulation to the left circulation and then to the brain.

The relationship between PFO and cryptogenic stroke has been demonstrated [1], but the exact mechanism remains unknown. The size and the funnel shape of the PFO are quite different to the simple hole of an ASD, and probably play an important role in this relationship.

In conclusion, contrast TCD is helpful in the selection of patients for PFO closure. Large R/L shunts seem to require PFO closure to prevent recurrent stroke events, but contrast TCD detected a high incidence of residual R/L shunts after PFO closure. However, the absence of recurrent stroke events after PFO closure, even in the presence of persisting R/L shunt, suggests that alteration of PFO configuration induced by transcatheter closure may prevent stroke. Further larger studies are needed to confirm these data.

Conflict of interest
None declared.

References


