

Does Transcatheter Closure of Patent Foramen Ovale Really “Shut the Door?”

A Prospective Study With Transcranial Doppler

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Background and Purpose—Transcatheter closure of patent foramen ovale (PFO) is increasingly being performed and monitored with transthoracic or transesophageal echocardiography, whereas contrast-enhanced transcranial Doppler (ce-TCD), which probably represents the most suitable tool to quantify right-to-left shunt (RLS) in the brain vessels, has been systematically overlooked. Our goal is to prospectively assess efficacy and safety of PFO transcatheter closure using ce-TCD.

Methods—A total of 140 consecutive patients (mean age, 46 ± 13 years; male/female ratio, 63/77) with PFO-related large RLS and no other recognized cause of focal cerebral ischemia underwent transcatheter closure. TCD was done preoperatively and 1 month after the procedure in all patients, after 3 months in 120, after 6 months in 112, and after 1 year in 104 patients.

Results—Implantation was successful in all patients. During Valsalva strain, a large shunt was still detectable in 31 of 140 (22%), 15 of 120 (13%), 9 of 112 (8%), and 9 of 104 (9%) patients at the 1-, 3-, 6-, and 12-month visits, respectively. Perioperative and postoperative complications included atrial fibrillation in 8% and scintillating scotomata in 6% of patients. During the 1-year follow-up period, only 1 transient ischemic attack was recorded in a patient with paroxysmal atrial fibrillation and complete PFO closure.

Conclusions—Transcatheter PFO closure in patients with cryptogenic stroke and large RLS may be less successful than reported previously. TCD appears the ideal tool to follow up the closure process and to identify early, during follow-up, those patients who will be left with a significant shunt. Atrial fibrillation is more common than believed previously and may underlie the occurrence of further cerebrovascular events despite complete PFO closure. Irritative visual phenomena may occur as a consequence of nickel toxicity. (*Stroke*. 2004;35:2140-2144.)

Key Words: foramen ovale, patent ■ stroke

Transcatheter patent foramen ovale (PFO) closure is a therapeutic option for patients with stroke of undetermined cause. The co-occurrence of large PFO, atrial septal aneurysm (ASA), and multiple events conveys a significant risk of relapse despite adequate medical treatment,¹⁻⁵ thereby indicating that closing PFO may protect patients against further embolic events.

However, PFO closure efficacy has been assessed only with transthoracic echocardiography (TTE) or, less often, transesophageal echocardiography (TEE),⁶⁻¹⁸ whereas contrast-enhanced transcranial Doppler (ce-TCD), which probably represents the most suitable tool to quantify right-to-left shunt (RLS) in brain vessels,^{1,19} has been systematically overlooked.

Therefore, we aimed to assess the efficacy of PFO transcatheter closure using ce-TCD to quantify the amount of RLS in a consecutive series of patients with cerebral ischemic lesions.

Materials and Methods

Starting in September 2001, all patients referred to the Department of Cardiology of the Humanitas Gavazzeni Clinic (F.C., E.O.) for transcatheter PFO closure after a stroke, transient ischemic attack (TIA), silent cerebral ischemia, or ≥ 1 episode of decompression sickness (DS) entered a combined study protocol that includes standardized history taking, a full neurological examination, computed tomography (CT) or MRI, the assessment of coagulation disorders, carotid ultrasound, TEE, and a ce-TCD (DWL Multidop) test by a team of neurologists (G.P.A., E.M.). All patients included must sign an informed consent form. The TCD test is performed according to a standardized procedure.²⁰ In brief, 10 mL of air-mixed saline was injected into the right antecubital vein while the Doppler signal from the right middle cerebral artery (MCA) during normal breathing and before a Valsalva maneuver were recorded. In case of RLS, air microbubbles are detected on the spectral display of the insonated artery and may be counted, allowing a quantitative assessment of the amount of shunt.²⁰ The proposed classification is as follows: small (< 10 bubbles) and large (> 10 bubbles) shunt with further subdivision of large shunts in “shower” (> 25 bubbles) and

Received March 31, 2004; final revision received May 31, 2004; accepted June 18, 2004.

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Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000137764.07815.de

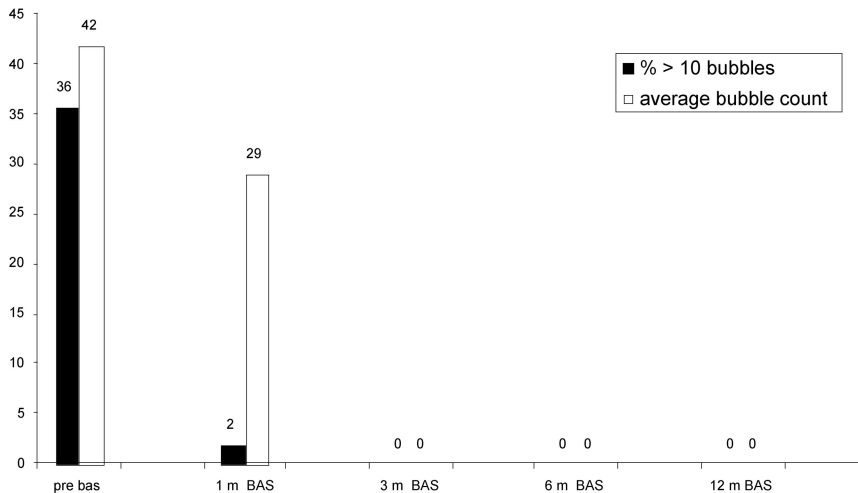


Figure 1. Quantification of spontaneous (BAS) RLS preoperatively and postoperatively at the 1-, 3-, 6-, and 12-month follow-up visits. Data from 104 patients with completed follow-up are shown. Black bars indicate the proportion of patients with large shunt (>10 bubbles). White bars indicate the average bubble count in patients with large shunt. BAS indicates basal (normal breathing).

“curtain” (uncountable signals) patterns. After this workup, patients with otherwise unexplained symptoms except for presumed paradoxical cerebral embolism who exhibit a large RLS undergo transcatheter closure of PFO and are followed up during regularly scheduled visits at 1, 3, 6, and 12 months postoperatively. During each follow-up visit, the clinical history is updated for possible adverse events or neurological symptoms, and TTE and ce-TCD are performed to assess correct placement of the occlusive device (TTE) and the degree of residual shunt (ce-TCD). To avoid potential bias in assessing the amount of RLS during the follow-up visits, TCD was performed first, with no knowledge of previous assessment results. The results of the first 140 patients studied so far are reported in this article.

Patients

A total of 63 males and 77 females were studied. Mean age was 46 ± 13 years. A total of 48 patients (35%) presented with TIA and 75 (55%) with a stroke between 3 and 6 months before closure. Two patients had retinal ischemia, and 12 presented with noncerebrovascular symptoms (angina in 4, acute myocardial infarction in 2, drop attack in 4, syncope in 2) but turned out to have ≥ 1 cerebral infarction, and 3 had ≥ 1 cerebral DS episode. CT scan or MRI disclosed no lesion in 46 (33%) patients, 1 lesion in 52 (37%), 2 lesions in 17 (12%), 3 lesions in 5 (4%), and >3 lesions in the remaining 20 (14%) patients. Risk factors for cerebrovascular diseases were hypertension in 26 (18.6%) patients, diabetes in 2 (1.4%), dyslipidemia in 30 (21.4%), current smoking in 23 (16.4%), migraine with aura in 26 (18.6%), previous venous troubles in 19 (13.6%), previous TIA in 6 (4.3%), and hyperhomocysteinemia in 12 (8.6%). Seven patients (5%) carried the G1691A mutation in the factor V gene (factor V Leiden), and 2 (1.4%) had moderately high titers of antiphospholipid antibodies. Sixty-six patients (47% of the whole cohort) showed an ASA on TEE.

PFO Closure

Under local anesthesia, PFO closure was performed after the standardized procedure, the details of which are described previously.²¹ Three occlusive devices were used: the Amplatzer PFO Occluder in 133 cases, the Gore-HELEX Septal Occluder in 4, and the PFO STAR in 3. Postprocedurally, each patient was prescribed 300 mg of aspirin daily for 6 months. Complete data were available for all 140 patients at 1 month, 120 at 3 months, 112 at 6 months, and 104 at 1 year.

Statistics

One-tailed *t* test statistics was used in comparisons between continuous variables.

Results

Procedural Outcome

Occlusive device deployment was successful in all cases. Perioperative complications occurred in 8 (5.7%) patients, which included transient coronary air embolism in 3 (2.1%), femoral hematoma in 4 (2.8%), and pericardial effusion requiring surgical drainage in 1 (0.7%).

PFO Closure

Before closure, a large shunt (ie, >10 bubbles recorded in the MCA) was present in 56 of 140 patients (40%) during normal breathing, with an average count of 56 microbubbles, and in all 140 patients after the Valsalva maneuver with an average number of 81 bubbles. Postoperatively, the proportion of patients with residual shunt during normal breathing was negligible during the first 3 months, whereas with Valsalva maneuver, still 22%, 13%, 8%, and 9% of patients exhibited a significant residual shunt at 1, 3, 6, and 12 months, with an average bubble load of 40, 36, 23, and 28, respectively. In summary, there was a progressive decline not only in the proportion of patients with persistent large shunts after the procedure but also in the average amount of the residual shunt during the first 3 months postoperatively, whereas no further improvement was observed thereafter. Further details can be drawn from the 104 patients who completed the 1-year follow-up (Figures 1 and 2). Among those still exhibiting a large shunt at 1 month ($n=18$), the average bubble count in the group that resulted in the 1-year complete closure ($n=9$; mean count 30 ± 20 bubbles) was not statistically different from the count in the group with persistent RLS at 1 year ($n=9$; mean count 25 ± 19 bubbles; $t=0.56$; $P=0.29$). However, at the 3-month follow-up, the average bubble count in the former dropped to 3 ± 4 , with no patient exhibiting >12 bubbles, whereas in the latter, it was still 22 ± 22 ($t=-2.51$; $P=0.016$).

Finally, in patients with persistent significant shunt at 1 year, the average preoperative bubble count was 45 ± 24 versus 28 ± 15 at 1 year ($t=1.61$; $P=0.07$).

Neurological Outcome

One patient had transient left arm numbness that occurred 3 weeks postoperatively during an episode of paroxysmal atrial

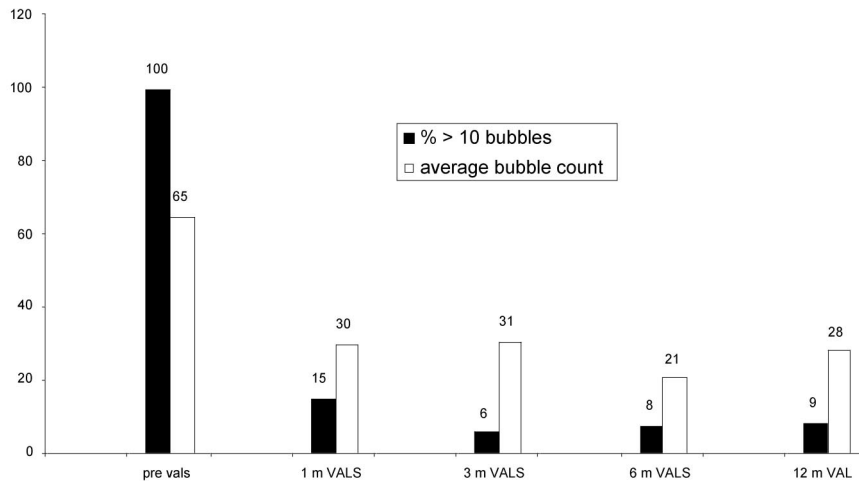


Figure 2. Quantification of Valsalva-driven (VALS) RLS preprocedurally and postprocedurally at the 1-, 3-, 6-, and 12-month follow-up visits. Data from 104 patients with completed follow-up are shown. Black bars indicate the proportion of patients with large shunt (>10 bubbles). White bars indicate the average bubble count in patients with large shunt.

fibrillation (AF). In this patient, the PFO was sealed at the 1-month follow-up.

Adverse Events

Subjective symptoms were common, including breathlessness and palpitations, which occurred mostly at the 1-month follow-up and subsequently declined but were still present at 12 months in 3 and 6 patients, respectively. Seven patients reported the novel occurrence of repetitive scintillating scotomata at the 1-month visit, without headache. One of them had experienced a single episode of migraine with aura during the past years, and 1 experienced migraine without aura.

During the first postoperative month, arrhythmia was detected in 13 patients, either because of subjective palpitations or at regularly scheduled electrokymogram: 1 had atrial extrasystolia, 2 had supraventricular paroxysmal tachycardia (in 1 patient this evolved to atrial flutter and required insertion of a permanent pacemaker), and 10 developed AF. Of them, 2 had paroxysmal AF at the end of the procedure, 1 the next day, and 7 within 1 month. However, all the patients had returned to sinus rhythm by the twelfth month (Table).

Discussion

Since the first report on transcatheter PFO closure in 1992,⁶ ≈1500 procedures have been reported. Periprocedural morbidity has been ≈8% for minor and 1.5% for major complications (the latter including death, cardiac tamponade requiring surgery, and massive pulmonary embolism),¹⁵ and failure to obtain an effective closure has ranged from 0% to 7%.^{7–12,14,18} Two exceptions are the recent reports by Kay et

al¹⁶ and Schwerzman et al¹⁷ in which the proportion of residual shunts was 18% at 2 years and 34% at 6 months after implantation of the Das AngelWings and the STAR devices, respectively. However, only 32 and 50 patients were included in the latter studies, underscoring the importance of the learning curve in this type of intervention.

As a rule, TTE and, less often, TEE have been used to assess PFO closure.^{7–18} In most cases, postprocedural thromboembolic events have been referred to recurrent paradoxical embolism through persistent patency of foramen ovale,^{8,9,11} mostly within the first postoperative year,^{8,12} but neurological relapses have also been reported in patients deemed closed.¹⁸

However, TTE has a low sensitivity in RLS detection,^{22,23} and the count of microbubbles in the left atrium with TEE after intravenous injection of agitated saline, which was commonly used to assess RLS amount, correlates poorly with the true PFO size.²³ Furthermore, criteria for PFO closure eligibility were usually not reported, and the timing of echocardiographic assessment with respect to the intercurrenting relapse was most often ill defined because patients were assessed retrospectively in the majority of published studies.¹⁵ For these reasons, the precise estimate of procedural success is often unclear, and interpretation of cerebrovascular events that occurred during the follow-up period is uncertain.

In this study, we included patients with PFO and cerebrovascular symptoms of otherwise unknown causes only if they exhibited a large shunt, and all patients were followed up prospectively at prespecified visits during which relevant clinical information was collected systematically and TTE and TCD were performed.

Our results indicate that the proportion of patients left with significant residual shunt at 1 year (9%) is in the rightmost end of the reported range.¹⁵ However, comparing our results with what is reported in the literature is difficult because different authors used different, mostly arbitrary, criteria to define residual shunts as significant on echocardiography.^{9,12} And in some reports, these are not even stated,^{8,10,11} whereas we adopted the TCD criterion, which has been shown to correlate with the occurrence or relapse of cryptogenic stroke.^{1,19} Although to the best of our knowledge, there are no data on the correlation between TCD and TEE in assessing

Adverse Event Recorded at the Scheduled Follow-Up Visits

	1 Month	3 Months	6 Months	1 Year
Breathlessness, n (%)	18 (15)	4 (3)	6 (5)	3 (3)
Palpitations, n (%)	38 (32)	14 (12)	4 (4)	6 (6)
Arrhythmia, n (%)	13 (11)	9 (8)	8 (7)	0 (0)
AF, n (%)	10 (8)	6 (5)	3 (3)	0 (0)
Scintillating scotoma, n (%)	7 (6)	4 (3)	1 (1)	1 (1)

the magnitude of RLS, it seems logical to assume that the larger the residual shunt on TEE, the higher the number of bubbles detected by TCD, whereas the opposite may not be the case because bubble above or below the scanning plane may be missed by TEE, and Valsalva strain may be insufficient. Therefore, the relatively high percentage of failures, compared with the literature, is to be ascribed to the greater sensitivity of the technique used to assess RLS (ce-TCD) and may represent the true incidence of residual shunt after a technically satisfactory procedure. This means that 1 in every 11 patients subjected to closure can be left with a significant shunt. However, our findings indicate that also in these patients, the procedure may be somehow beneficial because the amount of the residual shunt was almost halved at the twelfth month (45 ± 24 preoperatively versus 28 ± 15 at 1 year), although the difference was not statistically significant.

The second main finding is that the process of closure seems to follow a different time course in different patients. In slightly $<80\%$ of patients, the closure was complete within the first postoperative month, and $\approx 10\%$ of patients progressed further to closure in the next 2 months, whereas the remaining 10% did not show any further reduction by 1 year. Our data indicate that these patients may be identified quite early at the third postoperative month; in our series, no patient who resulted in complete closure at 1 year exhibited >12 microbubbles at 3 months, which can be taken as a cut-off value for an early prediction of failure.

Among variables that could influence the procedural success (gender, age, learning curve, anatomy of fossa ovalis), only the association with ASA tended to be over-represented in patients who failed to attain a full closure (67% in failed versus 40% in successful closures), but the small number of patients prevented any meaningful statistical comparison.

Reasons for persistent postprocedural shunt include not only failure to seal PFO but also the co-occurrence of pulmonary fistulas and abnormal venous return from coronary arteries. However, although TCD cannot reliably distinguish the site of the shunt,²⁴ it seems unlikely that extra cardiac conditions were responsible for the persistent shunts because all patients had TEE performed before intervention, which documented the direct passage of bubbles across the foramen ovale.

During the 1-year follow-up period, we recorded only 1 TIA in a patient with early complete closure of PFO but who had developed paroxysmal AF postoperatively. AF in our cohort occurred in 8% of patients at the 1-month visit and subsequently declined to 5%, 3%, and 0% at 3, 6, and 12 months, respectively. Compared with rates of 2%,¹² 3%,¹¹ and 1.9%¹⁸ reported by other authors, these figures are decidedly higher. Patients with PFO with or without ASA have an increased susceptibility to induced arrhythmia;^{25,26} therefore, it is surprising that cardiac rhythm abnormalities have been reported so rarely in the literature; indeed, in a number of articles, they are not even mentioned.^{7–10,13} We suspect that cardiac arrhythmias, and notably AF, may occur more frequently than reported previously, not only perioperatively^{11,12,18} but also in the early postoperative period. Reasons for underreporting of cardiac arrhythmias after transcatheter closure of PFO include retrospective design of

many reported studies and low index of suspicion. AF should be systematically sought, at least during the first postinterventional month.

To the best of our knowledge, scintillating scotoma has never been reported in the aftermath of PFO closure. This occurred in 6% of our patients at the 1-month follow-up, with the same characteristics of aura of migraine but with no previous history of migraine except in 1 case. As a rule, patients reported the sudden and repetitive onset of scintillations in the visual field with no side preference, lasting from seconds to ≈ 1 to 2 minutes and without further appearance of headache. Three patients were treated successfully with 200-mg bid of carbamazepine; in 4 others, no treatment was undertaken because of low frequency of the attacks, and in 3 of them, the disturbance resolved between the third and the sixth month postoperatively, but 1 had still rare attacks after 1 year.

Interpretation of this unexpected phenomenon is difficult; the fact that it tended to disappear in the first few months may be referred speculatively to irritation of the visual cortex produced by transient increased blood concentration of nickel.²⁷ However, we were not able to assess blood nickel concentration in these patients, and such an effect has never been reported among those related to nickel toxicity. Therefore, its exact pathophysiology remains unclear.

The main limitation of the present study is the fact that patients with residual shunt did not undergo a right heart catheterization to ascertain whether pulmonary fistulas were responsible for the residual postprocedural shunt. However, as discussed above, this seems an unlikely explanation for persisting postprocedural shunts.

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