

Outcomes After Transcatheter Closure of Patent Foramen Ovale in Patients With Paradoxical Embolism

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The purpose of the present study was to assess clinical outcomes and closure status after the transcatheter closure of patent foramen ovale. Two hundred thirty-seven consecutive patients (mean age 53 ± 15 years; 48% men) who underwent patent foramen ovale closure for the prevention of recurrent stroke were evaluated. Primary end points were death, recurrent stroke, and residual right-to-left shunt (RLS). Closure status was monitored at 1, 6, 12, 24, 36, and 48 months after the index procedure by power M-mode transcranial Doppler and was defined by the number of embolic tracks detected after the release of a sustained, calibrated Valsalva maneuver. During a mean follow-up period of 568 ± 364 days, the cumulative event rate for recurrent stroke ($n = 8$) was 3.4%, for an estimated event-free survival of 0.94 (SE 0.03). There was a significant difference in the estimated probability of recurrent stroke for patients grouped by age (≤ 55 years 1.4% vs > 55 years 6.6%, $p = 0.03$). There were 7 deaths (3.0%), 1 secondary to and 6 unrelated to recurrent strokes, and 3 surgical explantations (1.3%). Event-free survival, defined as freedom from death, stroke, or explantation, was 0.92 (SE 0.02). The magnitude of RLS was significantly less at late follow-up compared with baseline (grade 4.6 ± 0.7 vs 1.8 ± 1.6 , $p < 0.001$). Complete closure or minimal residual RLS (grade 0 to II) was achieved in 66% of patients. Device type (CardioSEAL or Amplatzer) did not affect the risk for adverse events or the presence of large residual RLS. In conclusion, transcatheter patent foramen ovale closure is associated with a low recurrent stroke rate in long-term follow-up. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:1312–1315)

The purpose of this investigation was to determine the longitudinal clinical outcomes and closure status in 237 consecutive patients with presumed paradoxical cerebral embolism who underwent transcatheter patent foramen ovale (PFO) closure at a single center. Primary end points included death, recurrent stroke, and the presence of residual right-to-left shunt (RLS) (i.e., closure status).

Methods

Design: This was an observational, single-center, repeated-measures study. Approval of the Western Institutional Review Board was obtained for the analysis of clinical data. From April 2001 to June 2005, all patients who underwent transcatheter PFO closure for stroke prevention at Swedish Medical Center (Seattle, Washington) were enrolled in a registry and received routine clinical care. Eligibility criteria for transcatheter PFO closure included a presumed paradoxical embolic event confirmed by computed tomography, magnetic resonance imaging, or clinical presentation; evidence of provokable RLS confirmed by power M-mode transcranial Doppler (pm-TCD) or transesophageal echocar-

diography; and probe patency of the septal tunnel during catheterization. For the purposes of this study, ischemic stroke was defined as an acute focal neurologic event with corresponding positive findings on magnetic resonance imaging, regardless of the duration of clinical symptoms; transient ischemic attack was defined as a temporary, reversible focal neurologic event without changes on magnetic resonance imaging. The presence of co-morbid conditions was extracted from patients' medical records. Hypertension was defined as systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg. Hyperlipidemia was defined as serum low-density lipoprotein > 130 mg/dl and/or serum triglycerides > 200 mg/dl.

Intracardiac echocardiography was used during the procedure to assess septal morphology and to identify the presence of atrial septal aneurysm. A single investigator (KAK) with expertise in pediatric and adult echocardiography analyzed the echocardiographic data and characterized septal morphology. Atrial septal aneurysm was defined as the presence of a localized protrusion of the fossa ovalis, with a base width ≥ 15 mm and mobile septal excursion ≥ 10 mm into the left or right atrium.¹ Before device implantation, a compliant sizing balloon was used to assess the diameter of the defect and to guide device size selection. After the procedure, antiplatelet therapy consisted of clopidogrel 75 mg for 3 months and acetylsalicylic acid 325 mg for ≥ 6 months.

Clinical follow-up and evaluation of closure status:

After PFO closure, clinical evaluation and pm-TCD with corresponding contrast transthoracic echocardiography were per-

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Table 1
Baseline clinical characteristics

Variable	All Patients (n = 237)	Age >55 Years (n = 91)	Age ≤55 Years (n = 146)
Age (yrs)	53 ± 15	69 ± 8	43 ± 9 [‡]
Men	48%	49%	48%
White	93%	95%	92%
Coronary artery disease	22%	29%	17%
Hypertension	43%	57%	34% [‡]
Hyperlipidemia	37%	45%	32% [*]
No. of previous cerebrovascular events	1.3 ± 0.6	1.4 ± 0.8	1.2 ± 0.5
History of >1 previous cerebrovascular event	26%	32%	23%
Isolated PFO	68%	57%	75%
Atrial septal aneurysm	32%	43%	25% [†]
Base pouch width (mm)	19.9 ± 5.3	19.0 ± 5.5	21.0 ± 4.9
Septal excursion (mm)	16.0 ± 4.8	16.2 ± 5.6	15.7 ± 3.9
Atrial septal defect	2.1%	2.8%	1.1%
PFO balloon waist diameter (mm)	13.0 ± 3.5	13.0 ± 3.9	13.0 ± 3.3
PFO septal tunnel length (mm)	11.3 ± 3.2	11.8 ± 3.7	10.9 ± 2.9
	During Normal Respiration	After Calibrated, Sustained Valsalva Maneuver	
Baseline interatrial RLS grade (all patients)			
0	14 (6%)	0	
I	21 (9%)	0	
II	36 (15%)	2 (0.9%)	
III	39 (16%)	15 (6%)	
IV	59 (25%)	54 (23%)	
V	56 (24%)	154 (65%)	

Data are expressed as mean ± SD or number (percentage).

* p = 0.035; † p = 0.005; ‡ p < 0.0001.

formed at 1, 6, 12, 24, 36, and 48 months. Patients who had neurologic symptoms were referred for neurologic evaluation. Death, ischemic stroke, peripheral embolism, and surgical device explantation were considered significant adverse events.

Because of its less invasive nature and comparable validity, pm-TCD was chosen over transesophageal echocardiography for the sequential evaluation of RLS.² Using a standardized technique,² agitated saline was injected into an antecubital vein of the supine patient during normal respiration and immediately after the release of a sustained (10 seconds), calibrated (40 mm Hg) Valsalva maneuver. The conductance of embolic tracks through an RLS to the middle and anterior cerebral arteries was monitored using bilateral pm-TCD. If the results were negative or inconclusive, a second injection was performed to verify the absence of shunt. Spontaneous or provoked RLS was semiquantitatively graded using a previously validated classification system (grade 0 = 0 embolic tracks, grade I = 1 to 10, grade II = 11 to 30, grade III = 31 to 100, grade IV = 101 to 300, and grade V = >300).² Closure status was based on the number of embolic tracks observed immediately after a sustained, calibrated Valsalva maneuver. Complete (i.e., satisfactory) closure was defined as <30 embolic tracks (grade 0

to II). Incomplete (i.e., partial) closure was defined as persistent RLS with detection of 31 to 100 embolic tracks (grade III). Large residual RLS was defined as >100 embolic tracks (grade IV or V). Contrast transthoracic echocardiography was performed at the time of pm-TCD to confirm the presence of intracardiac RLS and to evaluate device alignment and integrity, including the presence of thrombi.

Statistical analysis: Descriptive statistics were calculated for demographic and echocardiographic characteristics, the duration of follow-up, recurrent events, and RLS. Continuous variables are reported using the mean, range, SD, and 95% confidence interval; comparisons between patients aged ≤55 years and those aged >55 years were made using independent-samples Student's *t* tests. Levene's test was used to assess the equality of variances. Nominal and categorical data are reported as frequencies and percentages and were compared using chi-square analysis and Fisher's exact test for independent samples. Wilcoxon's signed-rank test was used for within-subject comparisons of serial RLS measurements. Spearman's rank correlation coefficients were calculated to assess the relation between baseline PFO characteristics and final pm-TCD RLS measurement. Kaplan-Meier survival analysis was used to assess the probability and SE of recurrent events after PFO closure, and the log-rank test was used to compare survival functions between age groups. Predictors of recurrent events were analyzed using the Cox proportional-hazards model. The level of significance was <0.05 (2 tailed). Statistical analyses were performed using SPSS Advanced Models version 12.0 (SPSS, Inc., Chicago, Illinois).

Results

During the study period, 237 consecutive patients (mean age 53 ± 15 years; 48% men) underwent transcatheter PFO closure for stroke prevention (Table 1). Patients aged ≤55 years (62%) constituted most of the sample. No significant differences were noted between the age groups in the degree of interatrial RLS at baseline. Of the 65 patients with transient ischemic attacks who underwent magnetic resonance imaging at baseline, 29 (45%) had normal findings, 8 (12%) had white-matter lesions, 26 (40%) had evidence of infarctions, and 2 (3%) had missing reports.

Using a transcatheter tunnel approach, a CardioSEAL (NMT Medical, Watertown, Massachusetts) or Amplatzer (AGA Medical Corporation, Golden Valley, Minnesota) septal occluder device was successfully deployed in 203 patients (86%) and 34 (14%) patients, respectively. Although 10 operators participated in the study, 208 of the devices (88%) were implanted by 3 operators (MR, WAG, JVO). Two serious catheter-related complications (0.8%) occurred: 1 device thrombus that resolved with short-term anticoagulation and the development of an arteriovenous fistula that required surgical intervention. There were no procedural deaths or complications requiring cardiac surgery or resulting in permanent disability.

Recurrent stroke and significant adverse events: The duration of follow-up was 568 ± 364 days. There were 7 late deaths (3.0%), only 1 of which was related to a new nontraumatic neurologic event. The remaining 6 deaths were unrelated

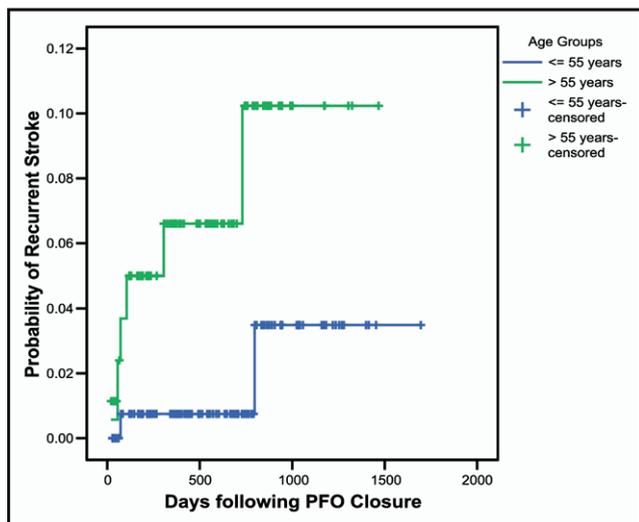


Figure 1. Cumulative estimated probability of recurrent stroke in patients who underwent PFO closure for stroke and had postclosure follow-up ($n = 212$), stratified by age. The *top curve* represents patients aged >55 years; the *bottom curve* represents patients aged ≤ 55 years. The estimated probability of stroke-free survival after a follow-up period of 568 ± 364 days was significantly different between patients aged ≤ 55 years and those aged >55 years (Kaplan-Meier analysis 0.97 vs 0.90, SE 0.03 and 0.04, respectively, $p = 0.03$).

to the procedure or to the risks of PFO (2 renal failure, 1 respiratory failure, 1 plane crash, 1 subdural hemorrhage related to fall, 1 ovarian cancer). No peripheral embolic events were observed in any of the patients after closure.

Eight of 237 patients (3.4%) who underwent PFO closure for the prevention of recurrent stroke or transient ischemic attack experienced clinically and radiographically confirmed strokes after PFO closure. At the time of their neurologic events, their international normalized ratios were 2.5 and 3.3. All 8 patients were taking aspirin at the time of their recurrent strokes; 2 (25%) were taking clopidogrel and aspirin, and 3 (38%) were taking warfarin and aspirin. Of these, 5 (62%) occurred within the first 4 months after closure. Two of the patients who were taking aspirin and warfarin had hemorrhagic strokes. An additional 5 patients (2.2%) reported having brief episodes of nonfocal transient neurologic symptoms (e.g., dizziness, headache, scintillating scotoma) and were referred for neurologic evaluation. On clinical exam, no residual neurologic symptoms were noted, and brain imaging findings were negative.

The cumulative estimated probability of a stroke-free survival rate after PFO closure for a duration of 568 ± 364 days was 0.94 (SE 0.02). There was a significant difference in stroke rate between patients on the basis of age group (≤ 55 years 1.4% vs >55 years 6.6%, $p = 0.03$; Figure 1). Age at the time of PFO closure was the only significant univariate predictor of recurrent stroke ($\beta = 0.076$, $p = 0.03$). There were no significant differences in the risk for recurrent stroke with respect to closure status, gender, history of multiple strokes, co-existing atrial septal aneurysm, or hypertension.

In the overall study group ($n = 237$), 3 septal occluder devices (1.3%) were surgically explanted in late follow-up because of device malalignment and large, persistent RLS that required surgical closure. All of the explants occurred

in women, who were implanted with 28-, 33-, and 40-mm CardioSEAL devices. None of the patients who experienced explantation had atrial septal aneurysms. After PFO closure, the cumulative adverse event rate for all-cause mortality ($n = 7$), recurrent stroke ($n = 8$), and surgical device explantation ($n = 3$) was 7.2%, which resulted in an estimated event-free survival of 0.92 (SE 0.04). One patient who died of a hemorrhagic stroke was included only in the death group for these calculations. All of the adverse events occurred in patients who received CardioSEAL devices; however, there was no significant difference between the type of PFO closure device deployed and the adverse event rate (chi-square 5.6, $p = 0.1$).

Interatrial shunt and final closure status: To determine the effect of PFO closure on RLS, pm-TCD was performed at baseline and repeated at 1, 6, 12, 24, 36, and 48 months after closure. Of the 237 patients in this cohort, 25 (11%) did not have pm-TCD evaluation after the procedure; therefore, residual RLS was undetermined in this subset. From baseline to 1 month after PFO closure, most patients (119 [72%]) had ≥ 2 -grade reductions in RLS, 46 (28%) had no significant changes in RLS (i.e., ± 1 grade), and 1 (1%) had a ≥ 2 -grade increase in RLS. Between 1 and 6 months, 78% of patients experienced no significant changes in RLS. However, 15% of patients had ≥ 2 -grade reductions in RLS 1 to 6 months after PFO closure, and 7% had ≥ 2 -grade increases in RLS. From 6 to 12 months after closure, 55 (82%) had no clinically important changes (± 1 grade) in RLS grade, whereas 8 (12%) had ≥ 2 -grade decreases in RLS and 4 (6%) had ≥ 2 -grade increases in RLS. One patient had a change from grade 0 to grade V from 6 to 12 months.

On final pm-TCD evaluation at 360 ± 267 days after PFO closure, complete closure or minimal RLS (grade 0 to II) was achieved in 140 patients (66%), whereas incomplete closure (grade III) was achieved in 42 (20%). Large (grade IV or V) RLS persisted in 30 patients (14%). In the 30 patients with large residual RLS, there was no significant difference between the proportion who received CardioSEAL closure devices and those who received Amplatzer devices (chi-square 1.686, $p = 0.9$). Patients with large residual RLS at final evaluation were more likely to have received closure devices ≥ 33 mm than those who did not have large residual RLS (57% vs 20%, $p = 0.001$). In comparison with baseline, final pm-TCD evaluation after PFO closure revealed a significant reduction in RLS grade (Valsalva 4.6 ± 0.7 vs 1.8 ± 1.5 , $Z = -11.7$, $p < 0.001$). The number of embolic tracks detected after a calibrated Valsalva maneuver at final pm-TCD evaluation was significantly correlated with baseline PFO balloon diameter ($r = 0.25$, $p < 0.01$). Coexisting atrial septal aneurysm was not associated with large residual RLS at final pm-TCD evaluation (large RLS 37%, nonlarge RLS 31%, $p = 0.53$).

Discussion

The results of this study indicate that the transcatheter closure of PFO is associated with a low risk for stroke recurrence (3.4% at 568 ± 364 days). This rate compares favorably with a 1-year thromboembolic event recurrence rate of 3.8% to 12.0% per year with medical therapy.³ Most recurrent stroke events (5 of 8 [63%]) occurred in the first 4

months after closure. Our results are consistent with those of other investigators, who reported recurrent event rates of 4% to 16% with long-term follow-up. Windecker et al⁴ reported a 4-year risk for combined transient ischemic attack, stroke, and peripheral embolism of 15.9%. As with our patient series, most adverse events occurred within the first year after closure. Increased age has not been associated with increased prevalence of recurrent stroke after PFO closure in all studies.^{4,5} Martin et al⁶ reported event-free incidences of 96% and 90% at 1 and 5 years, respectively. Wahl et al⁷ reported a 96% event-free survival rate at 5 and 10 years after PFO closure in their cohort of 450 patients. PFO closure was more effective at preventing recurrent events than medical therapy for patients with >1 cerebrovascular event at baseline or who had complete occlusion of PFO.⁸ Randomized trials are in progress to confirm these findings.

Echocardiography is used to diagnose PFO and evaluate residual RLS after closure. An early comparison study⁹ showed that transthoracic echocardiography was less than half as sensitive as transesophageal echocardiography, and single-gated transcranial Doppler was 68% as sensitive as transesophageal echocardiography in detecting RLS. More recently, pm-TCD showed 98% sensitivity with 94% accuracy in detecting PFO, whereas transesophageal echocardiography showed 91% sensitivity with 88% accuracy.² The lower sensitivity of transesophageal echocardiography to detect RLS in patients may be linked to sedation during the procedure, which hinders a patient's ability to perform an adequate and sustained Valsalva maneuver.^{10,11} Additionally, pm-TCD can detect almost twice as many embolic tracks as single-gated transcranial Doppler.² The timing and duration of the Valsalva maneuver,¹² the type of contrast injected, and patient position¹³ are all known to affect transcranial Doppler results. In addition, the depth of insonation is critical for the accurate measurement of embolic tracks.¹⁴ Pm-TCD evaluations were systematically performed using a standardized procedure² that controls for these variables and is consistent with the guidelines recommended by the international consensus meeting for transcranial Doppler.¹⁵ Absence of embolic tracks was confirmed by remeasurement. The improved sensitivity of TCD to detect RLS may be 1 reason for the increased incidence of residual RLS in this study and in the study by Anzola et al,¹⁶ compared with other investigators who used transesophageal echocardiography to assess closure status.¹⁷

The results of the present study are limited in their generalization to the larger PFO population. There was no effort to rule out alternative sources of RLS (e.g., pulmonary arteriovenous malformation) in patients. It is possible that some residual RLS were due to such a defect. It is possible that recurrent stroke occurring in the early postclosure period, before device endothelialization, could have been secondary to embolism from the device despite antiplatelet and anticoagulation therapy and was undetected by transthoracic echocardiography. There was no randomization of patients to treatment groups and a relatively small sample size. Data were not collected on the time between the initial cerebrovascular event and the date of closure. A

small number of patients had recurrent stroke after PFO closure, which confounded the statistical analysis.

In conclusion, transcatheter PFO closure does not increase and may decrease the risk for recurrent stroke during long-term follow-up. Prospective randomized trials are needed to confirm the success of transcatheter PFO closure in the prevention of recurrent cerebrovascular events.

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