

Frequency of Migraine Headache Relief Following Patent Foramen Ovale “Closure” Despite Residual Right-to-Left Shunt

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Retrospective studies have shown improvement in migraines after patent foramen ovale (PFO) closure. To date, no study has evaluated whether the completeness of closure affects headache status; therefore, the objective of this study was to evaluate the impact of residual right-to-left shunt (RLS) on migraine symptoms after transcatheter PFO closure in migraineurs with and without aura. This was a small-series, single-center, retrospective analysis of late follow-up data on 77 patients with presumed paradoxical embolism and migraine who underwent PFO closure for secondary stroke prevention. Power M-mode transcranial Doppler was used to assess RLS at baseline and 6 and 12 months after closure. A standardized migraine questionnaire was administered at baseline and 6, 12, and 24 months after closure. Fifty-five (71%) patients had migraine with aura. Final closure and migraine status were available for 67 patients; 23 (34%) had incomplete PFO closure, defined as 30 embolic tracks detected at final power M-mode transcranial Doppler examination (median 366 days, 95% confidence interval 332 to 474). Migraine relief ($\geq 50\%$ reduction in frequency) was independent of closure status (77% complete closure vs 83% incomplete closure, $p = 0.76$) at late follow-up (540 days, 95% confidence interval 537 to 711). Migraineurs with aura were 4.5 times more likely to experience migraine relief than migraineurs without aura. In conclusion, migraine relief may occur despite residual RLS after transcatheter PFO closure, which may suggest a reduction in RLS burden below a neuronal threshold that triggers migraine; however, this warrants further investigation. Migraine with aura may be an independent predictor of relief after PFO closure. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;102:916–920)

Depending on the diagnostic method used, moderate to large residual right-to-left shunt (RLS) occurs in 1% to 34% of patients >1 year after patent foramen ovale (PFO) closure.^{1–3} The effect of residual RLS on migraine relief has not been clearly established. Azarbal et al⁴ reported no differences in migraine relief experienced by patients with and without residual RLS at 12 months after closure. In our previous analysis⁵ of 50 migraineurs (mean follow-up 37 ± 23 weeks), final PFO closure status did not influence migraine relief ($p = 0.91$). In contrast, Schwerzmann et al⁶ found that 3 of 7 migraineurs (43%) with aura who had no improvement in headache symptoms after PFO closure had large residual RLS, on the basis of measurement using transesophageal echocardiography (TEE). The primary aim of this study was to determine if migraine relief after PFO closure occurs in the presence of residual RLS on late (≥ 12 months) follow-up. We hypothesized that migraine relief would not be dependent on complete closure (i.e., complete elimination vs reduction of RLS). The secondary aim of the study was to compare migraine relief in migraineurs with

and without aura. Primary end points were final closure status and migraine frequency per month.

Methods

This was a single-center, retrospective, repeated-measures study. Approval of the Western Institutional Review Board (Olympia, Washington) was obtained for the analysis of clinical data. This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. From April 2001 to June 2005, all patients who underwent transcatheter PFO closure for the prevention of recurrent cerebrovascular events at Swedish Medical Center (Seattle, Washington) were enrolled in a PFO registry and received routine clinical care. Eligibility criteria for transcatheter PFO closure included a presumed paradoxical cerebral embolic event confirmed by computed tomography or magnetic resonance imaging and clinical presentation; evidence of provokable RLS confirmed by contrast-enhanced, bilateral power M-mode transcranial Doppler (pmTCD) and/or TEE; and probe patency of the septal tunnel during catheterization.

Intracardiac echocardiography was performed during PFO closure (Acuson AcuNav; Siemens Medical Systems, San Diego, California) to evaluate PFO tunnel length, balloon-stretch diameter, and the presence of coexisting atrial septal aneurysm and atrial septal defect.⁷ A compliant, conforming sizing balloon was used to assess PFO diameter to guide device size selection. Balloon inflation was completed

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Table 1
Baseline and procedural characteristics

Variable	Migraineurs With Aura (n = 55)	Migraineurs Without Aura (n = 22)	p Value
Women	42 (76%)	15 (68%)	0.57
Age (yrs)	47 ± 12	46 ± 10	0.49
White	52 (95%)	21 (96%)	0.81
Coronary artery disease	12 (22%)	3 (14%)	0.53
Hypertension*	23 (42%)	7 (32%)	0.45
Hyperlipidemia†	15 (27%)	6 (27%)	1.00
Stroke (history)	38 (69%)	15 (68%)	0.57
Transient ischemic attack (history)	30 (55%)	9 (41%)	0.20
Recurrent cerebrovascular events (history)	14 (26%)	7 (32%)	0.58
Hypercoagulable state (n = 59)	17 (40%)	5 (31%)	0.76
Anticoagulation and/or antiplatelet (aspirin, clopidogrel, aspirin/extended-release dipyridamole) therapy at baseline	51 (93%)	20 (91%)	0.19
Migraine frequency per month	5.1 ± 7.5	4.8 ± 6.7	0.32
Migraine severity (0 to 10)	7.3 ± 2.4	7.6 ± 2.2	0.68
PFO balloon waist diameter (mm)	13.2 ± 3.2	12.3 ± 3.5	0.27
PFO septal tunnel length (mm)	10.9 ± 3.4	10.2 ± 2.7	0.41
Atrial septal aneurysm	18 (33%)	8 (36%)	0.79
Device type			
CardioSEAL	45 (82%)	22 (100%)	
Amplatzer	10 (18%)	0 (0%)	
Device size (mm)			
23	12 (22%)	9 (41%)	
28	18 (33%)	5 (23%)	
≥33	15 (27%)	7 (32%)	0.25
Large RLS, rest (grade IV-V/V) (n = 72)	28 (54%)	16 (80%)	0.06
Large RLS, Valsalva (grade IV-V/V) (n = 72)	51 (98%)	20 (100%)	1.00

Data are expressed as mean ± SD or as frequency (percentage). The p values are based on independent-samples Student's *t* tests for continuous data and chi-square or Fisher's exact tests for categorical data.

* Systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg.

† Serum low-density lipoprotein >130 mg/dl and/or serum triglycerides >200 mg/dl.

when the PFO tunnel was completely occluded and a small waist was visible on intracardiac echocardiography. The inflated balloon waist diameter was measured with the aid of calibrations on the sizing balloon. Septal tunnel length was measured as the distance between the right and left atria. Atrial septal characteristics were evaluated postprocedurally by a single cardiologist (KAK) with expertise in TEE and intracardiac echocardiography, who was blinded to patient migraine status. Atrial septal aneurysm was defined as a localized protrusion of the fossa ovalis, with a base width >15 mm and mobile septal excursion into the left or right atrium >10 mm.⁸ Atrial septal defect was defined as a predominant left-to-right shunt at rest, on the basis of color-flow Doppler interrogation. One patient with a coexisting atrial septal defect was excluded from the final analysis. After the procedure, antiplatelet therapy consisted of clopidogrel 75 mg for 3 months and aspirin 325 mg for ≥6 months.

All patients underwent neurologic evaluation before PFO closure as routine standard of clinical care. Patients were diagnosed with active migraine with or without aura by a neurologist according to the International Headache Society diagnostic criteria.⁹ Information was collected from medical records and a patient questionnaire that assessed standardized migraine information (i.e., frequency, severity, and duration).

The primary end points of this study were final closure status and the number of migraine events per month. Clinical evaluation and pmTCD were performed 6 and 12 months after PFO closure. Patients completed a standardized migraine symptom questionnaire at 6, 12, and 24 months after closure. Migraine relief was assessed according to change in the frequency of migraine events per month and classified as complete relief, substantial relief (≥50% reduction), no relief (<50% reduction), or worse (≥50% increase). For the purposes of analysis, migraine relief was defined as a ≥50% reduction in migraine frequency (the sum of the complete and substantial relief subgroups). Final migraine status was not determined until ≥6 months after PFO closure.

Because of its less invasive nature and comparable validity with TEE,¹⁰ pmTCD was used for the sequential evaluation of RLS before and after PFO closure. Patients underwent bilateral pmTCD examinations of the middle and anterior cerebral arteries using a 100M digital 2-MHz Doppler platform (Spencer Technologies, Seattle, Washington). Using a standardized technique,¹⁰ agitated saline was injected into an antecubital vein during normal respiration and immediately after a calibrated (40 mm Hg), sustained (10 seconds) Valsalva maneuver. Embolic tracks were monitored for 1 minute. If the results were negative or inconclusive, a second injection was performed to verify the absence

of RLS. Spontaneous or provoked RLS was graded using a validated classification system for embolic tracks (grade 0 = 0, grade I = 1 to 10, grade II = 11 to 30, grade III = 31 to 100, and grade IV = 101 to 300).¹⁰ If embolic tracks were too numerous to count (shower or curtain effect), the result was recorded as 301 embolic tracks, or grade V.¹⁰ Final closure status was based on the number of embolic tracks observed after the Valsalva maneuver. Complete closure was defined as ≤ 30 embolic tracks (grades 0 to II), and incomplete closure was defined as persistent RLS of >30 embolic tracks (grades III to V). Contrast transthoracic echocardiography was performed concurrently with pmTCD to confirm presence of intracardiac RLS, evaluate device alignment and integrity, and assess the presence of thrombi.

Descriptive statistics were used for demographic and co-morbidity data, atrial septal characteristics, and RLS measurements. Continuous variables are reported as mean \pm SD or medians and 95% confidence intervals (CIs). Nominal and categorical data are reported as frequencies and percentages. Normality was assessed by examining stem-and-leaf plots and histograms and statistically evaluated using the Kolmogorov-Smirnov test. The association between migraine relief and closure status was analyzed using Pearson's chi-square tests. Differences in final migraine frequency and RLS reduction between the closure groups were analyzed with independent Student's *t* tests and analysis of variance with post hoc multiple comparisons; reductions in migraine frequency from baseline to final follow-up were analyzed with paired Student's *t* tests. Differences between migraineurs with and without aura were evaluated using independent-sample Student's *t* tests, Fisher's exact tests, and chi-square tests. Binary logistic regression was used to calculate the odds ratio of migraineurs with aura experiencing migraine relief compared with migraineurs without aura. The threshold for statistical significance was set at $p = 0.05$ (2 tailed). Statistical analyses were performed using SPSS Advanced Models version 15.0.1 (SPSS, Inc., Chicago, Illinois) and Sample Power version 2.0 (SPSS, Inc.).

Results

Seventy-seven of 246 registry patients (31%) met International Headache Society criteria for active, recurrent migraine⁹; of these, 55 (71%) had migraine with aura. The 2 migraine groups had similar demographic and baseline co-morbidities, migraine frequency per month, migraine severity, and baseline atrial septal characteristics (Table 1). The first 5 migraineurs who underwent PFO closure did not have baseline pmTCD evaluation ($n = 72$). At baseline, 28 of 52 migraineurs with aura (54%) had large RLS (grade IV or V) at rest, compared with 16 of 20 migraineurs without aura (80%) ($p = 0.06$). Fifty-one of 52 migraineurs with aura (98%) and 100% of migraineurs without aura had large RLS immediately after the Valsalva maneuver ($p = 1.00$). CardioSEAL (NMT Medical, Watertown, Massachusetts) or Amplatzer (AGA Medical Corporation, Golden Valley, Minnesota) devices were deployed by the transcatheter tunnel approach in 67 patients (87%) and 10 patients (13%), respectively. The PFO registry was closed before completing 6-month follow-up for 5 patients; thus, final migraine and closure data were available for 67 patients. The median

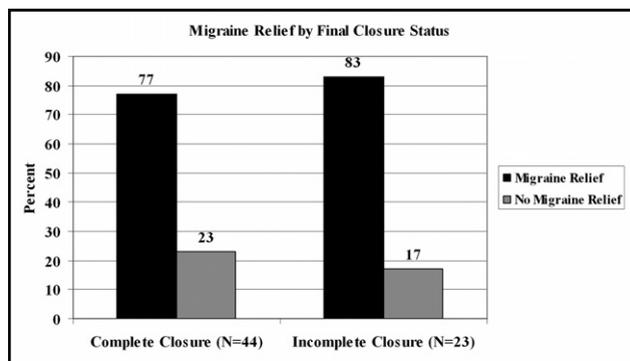


Figure 1. Migraine relief was independent of final closure status (chi-square = 0.26, $p = 0.61$ between complete and incomplete closure groups). Complete closure was defined as ≤ 30 embolic tracks detected by pmTCD; incomplete closure was defined as >30 embolic tracks detected by pmTCD. Migraine relief was defined as $\geq 50\%$ reduction in migraine frequency; no migraine relief was defined as $<50\%$ reduction in migraine frequency.

duration of clinical follow-up was 540 days (95% CI 537 to 711); 47 patients (70%) had follow-up >420 days after PFO closure.

After PFO closure, patients experienced significantly reduced migraine frequency (from 4.4 ± 6.3 to 1.7 ± 4.5 events/month, $p < 0.001$). Thirty-six migraineurs (54%) experienced complete migraine relief, 17 (25%) experienced substantial relief, 11 (16%) reported no relief, and 3 (5%) reported $\geq 50\%$ increases in migraine frequency. In the 31 patients (46%) who continued to experience migraines after PFO closure, migraine frequency decreased from 5.8 ± 7.7 to 3.7 ± 6.2 per month ($p < 0.001$).

Patients were classified as having either complete ($n = 44$ [66%]) or incomplete ($n = 23$ [34%]) closure at final pmTCD examination (median 366 days, 95% CI 332 to 474). If no embolic tracks were detected at 6 months after closure, patients were determined to have complete closure, and subsequent pmTCD examinations were not performed. Of the patients who experienced complete closure, 22 (50%) reported complete migraine relief, 12 (27%) reported substantial relief, 9 (20%) reported no change, and 1 (2%) reported a $\geq 50\%$ increase in migraine frequency. Of the patients who experienced incomplete closure, 14 (61%) reported complete relief, 5 (22%) reported substantial relief, 2 (9%) reported no change, and 2 (9%) had $\geq 50\%$ increases in migraine frequency. There was no significant difference in the proportion of patients with complete versus incomplete closure who experienced migraine relief (77% vs 83%, respectively, $p = 0.76$; Figure 1). The mean reduction in embolic tracks after PFO closure was not different between patients who reported migraine relief and those who continued to experience migraine symptoms (243 ± 101 vs 182 ± 159 embolic tracks, respectively, $p = 0.10$). There was no difference in final migraine frequency between complete and incomplete closure groups (2.0 ± 5.4 vs 1.0 ± 1.8 per month, respectively, $p = 0.25$). With sample sizes of 44 and 23 for the 2 groups, the study yielded a power of 0.15 to detect a significant difference in migraine relief (chi-square $p < 0.05$).

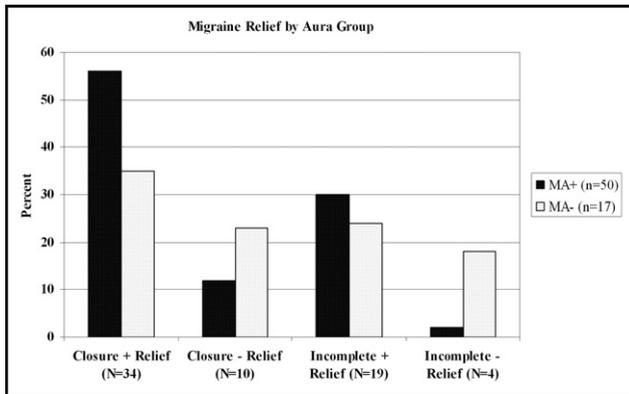


Figure 2. Migraine relief by aura group. Migraineurs with aura (MA+) experienced significantly more migraine relief than migraineurs without aura (MA-) (chi-square = 5.67, $p = 0.03$). Complete relief was defined as migraine resolution, substantial relief as $\geq 50\%$ reduction in migraine frequency, no relief as $< 50\%$ reduction in frequency, and worse as $\geq 50\%$ increase in frequency.

Omnibus analysis of variance revealed significant between-group differences for percentage change in RLS from baseline and migraine relief ($p < 0.001$). Post hoc multiple comparisons showed that patients with migraine relief but incomplete closure had significantly lower percentage changes in RLS compared with patients with migraine relief and complete closure ($52 \pm 41\%$ vs $99 \pm 2\%$, respectively, $p = 0.001$) and patients without migraine relief and complete closure ($98 \pm 3\%$, $p = 0.002$).

There was a significant difference in migraine relief experienced by migraineurs with aura compared with those without aura (Figure 2). Forty-three migraineurs with aura (86%) reported migraine relief compared with 10 migraineurs without aura (59%) (chi-square = 5.7, $p = 0.03$), despite a similar degree of complete closure (68% migraineurs with aura vs 59% migraineurs without aura, $p = 0.56$). Migraineurs with aura were 4.6 times more likely than migraineurs without aura to experience relief after PFO closure (logistic regression, 6.4 and 1.4, respectively, $p = 0.02$).

Discussion

The results of the present study extend the findings of our 2005 study⁵ by showing that clinically significant migraine relief after PFO closure occurred despite residual RLS on late follow-up. Migraine relief was seen in 77% and 83% of patients with complete and incomplete closure, respectively. Gori et al¹¹ reported that the degree of RLS before PFO closure did not correlate with migraine symptom severity and postulated that RLS might be an "all or nothing" phenomenon that causes migraine. The relief experienced by patients with incomplete PFO closure in the present study contradicts that hypothesis.

Current theories of migraine pathogenesis in patients with PFO suggest that microemboli or vasoactive chemicals, normally eliminated by the pulmonary filter, are conducted to the cerebral circulation. Compared with nonmigraineurs, migraineurs have increased platelet activation and aggregation in response to serotonin,^{12,13} which is metabolized by pulmonary monoamine oxidase.¹⁴ Serotonin may

be shunted to the systemic circulation through the PFO to trigger cortical spreading depression and precipitate aura.^{15,16} Alternately, microemboli in the venous circulation may be transmitted through the PFO and trigger cortical spreading depression.¹⁷ A reduction in RLS after PFO closure would reduce the amounts of these substances that are conducted to the cerebral vasculature. Cerebral ischemia and reduced regional cerebral blood flow are associated with cortical spreading depression and may lead to trigeminovascular system activation and headache pain.¹⁸

Larger RLS may increase migraine probability,^{19,20} suggesting a "neuronal threshold" above which migraine is triggered. Tembl et al²¹ reported that 51.5% of migraineurs with aura and massive RLS (defined as > 25 microbubbles detected using unilateral transcranial Doppler) had headaches triggered by Valsalva-provoking activities; however, only 1 of 15 migraineurs (7%) who reported Valsalva-induced headaches in another study²² had PFOs. Almost all (99%) patients in the present study had large RLS at baseline, which indicates selection bias. Migraine is linked to cortical hyperexcitability,¹⁸ and repetitive exposure to emboli or chemicals through spontaneous RLS may reduce the neuronal threshold and increase migraine susceptibility.^{17,18} We theorize that reduction in spontaneous RLS may decrease the amount of migraine and neuronal hypersensitivity. This finding warrants further investigation.

Thirty-four percent of patients in the present study experienced incomplete PFO closure (i.e., residual RLS) on late follow-up on the basis of pmTCD, which is higher than in reports that assessed closure status using TEE.^{1,3} Some patients in the present study may have had secondary source of RLS (e.g., pulmonary arteriovenous malformation). In a preliminary study, 35% of patients who underwent PFO closure had secondary sources of RLS, on the basis of pmTCD evaluation during balloon sizing of the PFO²³; thus, we cannot infer that the presence of residual RLS was due solely to incomplete PFO closure. A large number of patients (29%) were implanted with devices ≥ 33 mm in diameter, which may not have secured the interatrial septum, especially in patients with atrial septal aneurysms.

The results of this study, although underpowered, suggest that migraine with aura is an independent predictor of migraine relief after PFO closure. Previous studies^{3-5,24} have reported no differences in relief between migraineurs with and without aura. Our earlier report⁵ was based on fewer patients ($n = 50$) and a shorter duration of follow-up (37 ± 23 weeks). The reduction in RLS would account for the complete relief experienced by most migraineurs with aura after closure. Patients who did not experience migraine relief despite sizable RLS reduction ($n = 19$ [28%]) may have had different mechanisms of migraine pathology. Because migraineurs without aura and nonmigraineurs have a similar prevalence of PFO,¹⁸ it has been suggested that migraine without aura is more influenced by environmental factors than migraine with aura.²⁵ Our findings suggest that migraine with aura is a potential selection criterion for randomized PFO closure trials. This observation is supported by a retrospective study²⁶ in which migraineurs with aura and PFOs were more likely to have recurrent cerebrovascular events than migraineurs without aura or nonmigraineurs (odds ratio 3.87, 95% CI 1.75 to 8.50). Thus, PFO

closure in migraineurs with aura may provide headache relief and protection from recurrent stroke.

The results of this study may have been affected by recall bias and placebo effect. It is possible that patients with migraine relief are more motivated to adhere to follow-up than those without relief. Complete data were not available on 10 patients because of a lack of baseline pmTCD examination (n = 5) or <6 months of follow-up data (n = 5). The migraine relief in the present study exceeded the threshold of 35% to 40% for therapeutic effect recommended for open-label, placebo-controlled migraine prophylaxis studies.²⁷ It is also possible that PFO closure (whether complete or incomplete) has no effect on migraine frequency, on the basis of the results of the first prospective, randomized study of PFO closure in migraine,²⁸ although we believe that these 2 studies had different migraine populations. Because symptomatic paradoxical embolism was the impetus for PFO closure, our study population may have had larger baseline RLS and thus may represent selection bias. Migraineurs with previous stroke reportedly have a significantly higher number of embolic tracks than migraineurs without previous stroke²⁰; therefore, migraineurs in the present study may have had a greater reduction in headaches in response to PFO closure.

This retrospective study was also limited by the effect of the antiplatelet regimen patients took after the procedure, the natural variability of migraine, and the decrease in migraine frequency after stroke²⁹ and the fourth decade of life. Changes in migraine prophylactic medications after PFO closure were not captured. Before PFO closure, 92% of patients took anticoagulant and/or antiplatelet medications. Nevertheless, the median final follow-up period of 540 days extended beyond the discontinuation of antiplatelet medications at 6 months, which suggests that PFO closure has a significant and lasting impact on migraine frequency.

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