

Migraine Headache Relief After Transcatheter Closure of Patent Foramen Ovale

Mark Reisman, MD,* Ryan D. Christofferson, MD,* Jill Jesurum, PhD,* John V. Olsen, MD, FACC,* Merrill P. Spencer, MD,† Kimberly A. Krabill, MD,* Lance Diehl, MD,* Sheena Aurora, MD,* William A. Gray, MD*

Seattle, Washington

OBJECTIVES	The purpose of this study was to determine the effects of transcatheter patent foramen ovale (PFO) closure on migraine frequency in patients with paradoxical cerebral embolism.
BACKGROUND	The prevalence of migraine headache is higher in cryptogenic stroke patients with PFO than in the general population. Previous studies have suggested that closure of the PFO may reduce migrainous symptoms.
METHODS	Between April 2001 and December 2003, 162 consecutive patients with paradoxical cerebral embolism underwent transcatheter PFO closure for prevention of recurrent cryptogenic stroke or transient ischemic attack. A one-year retrospective analysis of migraine symptoms before and after PFO closure was performed.
RESULTS	Active migraine was present in 35% (57 of 162) of patients, and 68% (39 of 57) experienced migrainous aura; 50 patients were available for analysis at one year. Complete resolution of migraine symptoms occurred in 56% (28 of 50) of patients, and 14% (7 of 50) of patients reported a significant ($\geq 50\%$) reduction in migraine frequency. Patients reported an 80% reduction in the mean number of migraine episodes per month after PFO closure (6.8 ± 9.6 before closure vs. 1.4 ± 3.4 after closure, $p < 0.001$). Results were independent of completeness of PFO closure at one year.
CONCLUSIONS	In patients with paradoxical cerebral embolism, migraine headaches are more frequent than in the general population, and transcatheter closure of the PFO results in complete resolution or marked reduction in frequency of migraine headache. (J Am Coll Cardiol 2005;45:493-5) © 2005 by the American College of Cardiology Foundation

Migraine headache is a common, often disabling, condition and represents a significant health care burden. Recent evidence has shown that migraineurs who experience an aura beforehand are twice as likely to have a patent foramen ovale (PFO) (41% to 48%) than the general population (16% to 20%) (1,2). Right-to-left cardiac shunt at rest through a PFO also is more common in migraineurs with aura (15%) than in control patients with PFO who do not experience migraines (0%) (1), suggesting that interatrial communication may play a role in the pathogenesis of migraines.

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Previous publications have demonstrated closure of the PFO in patients with cryptogenic stroke or decompression illness may reduce migraine symptoms (3-6). The purpose of this study is to report the effect of transcatheter PFO closure on migraine frequency in patients with presumed paradoxical cerebral embolism.

METHODS

The study was descriptive, correlational, and retrospective. The Western Institutional Review Board approved the

retrospective analysis. Between April 2001 and December 2003, 162 consecutive patients with presumed paradoxical embolism underwent transcatheter PFO closure to prevent recurrent stroke or transient ischemic attack. Eligibility criteria included a presumed paradoxical thromboembolic event evidenced by clinical and/or radiologic findings (computed tomography, magnetic resonance imaging, or angiogram) and a provokable right-to-left shunt, confirmed by contrast, bilateral power m-mode transcranial Doppler (pm-TCD) and/or transesophageal echocardiography (7).

Using a percutaneous, transcatheter approach, a septal occluder device was implanted successfully in all patients. Thereafter, daily antiplatelet therapy consisted of 75 mg of clopidogrel for three months and 325 mg of aspirin for six months. Symptom and standardized migraine questionnaires were administered at baseline and in follow-up to assess cardiac and neurologic status. Migraine events were classified according to International Headache Society criteria (8). Migraine definitions of relief following closure were defined as: 1) complete absence of symptoms; 2) significant, that is, $\geq 50\%$ reduction in monthly frequency; and 3) minimal/none, that is, $< 50\%$ reduction in monthly migraine frequency.

Closure status and residual right-to-left shunt were evaluated serially using pm-TCD with measurements during resting respiration and calibrated Valsalva. Final closure status was based on the number of embolic tracks observed during calibrated Valsalva.

From the *Cardiovascular Research, Swedish Medical Center, and †Spencer Vascular Laboratories, Seattle, Washington.

Manuscript received June 11, 2004; revised manuscript received October 14, 2004, accepted October 18, 2004.

Abbreviations and Acronyms

PFO = patent foramen ovale
pm-TCD = power m-mode transcranial Doppler

Statistical analysis. Data are reported as means \pm standard deviations. Pearson chi-square, and independent samples *t* test and paired-samples *t* tests were used to compare categorical, nominal, and continuous variables, respectively. Early and late follow-up of migraine frequency were compared using a within-subjects repeated-measures analysis of variance. Assumptions of normality and homogeneity of variance were satisfied. The level of significance for all tests was set at 0.05 (two-tailed). Data were analyzed using the Statistical Package for the Social Sciences (version release 11.0.1, SPSS Inc., Chicago, Illinois).

RESULTS

Thirty-five percent (57 of 162) of patients experienced active migraine symptoms at the time of PFO closure and, of these, 68% (39 of 57) had a history of migrainous aura. Table 1 shows that patients with migraine were younger, more likely to be female, and more likely to have a large shunt (>100 embolic tracks using pm-TCD) at rest (*p* < 0.05) than patients without migraine. There were no significant differences (*p* = NS) in the baseline characteristics of migraineurs who experienced an aura beforehand (*n* = 39) and those who did not experience aura (*n* = 18). Within the migraine group, 7 patients had incomplete follow-up; therefore, 50 migraineurs were included in the final analysis (*n* = 50).

At a mean duration of follow-up of 37 ± 23 weeks, patients reported significantly fewer migraine episodes/month (6.8 ± 9.6 before closure vs. 1.4 ± 3.4 after closure, *p* < 0.001). Migraine symptoms were completely relieved in 56% (28 of 50) and significantly ($\geq 50\%$) reduced in 14% (7 of 50) of patients. Fifteen (30%) patients reported minimal

Table 1. Baseline Patient and Procedural Characteristics

	Nonmigraineurs (n = 105)	Migraineurs (n = 57)
Demographic data		
Age (yrs)*	58 \pm 17	47 \pm 12
Female*	48 (46%)	38 (67%)
Procedural characteristics		
Co-existing atrial septal aneurysm†	31 (30%)	14 (25%)
PFO balloon waist size, mm	13.2 \pm 3.8	12.9 \pm 2.9
Device size, mm	28.7 \pm 5.6	27.8 \pm 5.4
Closure device type		
NMT CardioSEAL	99 (94%)	52 (91%)
AGA Amplatzer	6 (6%)	5 (9%)
Transcranial Doppler data (n = 147)		
Large shunt at rest*‡	35/95 (37%)	28/52 (54%)
Large shunt at Valsalva*‡	82/95 (86%)	50/52 (96%)

Values are n (%) or mean \pm SD. *Significance to *p* < 0.05. †Protrusion of the interatrial septum with a base width ≥ 15 mm and mobile excursion ≥ 10 mm. ‡More than 100 embolic tracks.

PFO = patent foramen ovale.

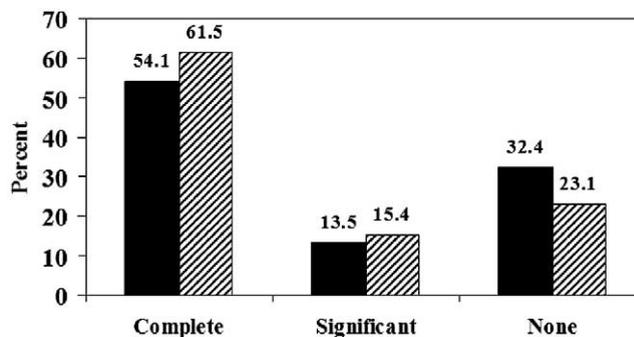


Figure 1. Migraine headache relief by migraine subtype according to presence or absence of aura. Significant relief (Significant) = $\geq 50\%$ reduction in monthly migraine frequency. No relief (None) = <50% reduction in monthly migraine frequency. Chi-square test = 0.40, *p* = 0.82 for the comparison between groups. Solid bars = migraine with aura (*n* = 38); hatched bars = migraine without aura (*n* = 12).

(<50%) or no relief of migraine symptoms. In a subgroup of 21 patients who had serial assessment of migraine frequency at early (18 ± 17 weeks) and late follow-up (40 ± 26 weeks), no significant differences in monthly migraine frequency were found between early (1.6 ± 3.7) and late (1.1 ± 2.6) follow-up (*F* = 1.69, *p* = 0.208), suggesting a persistent treatment effect. The degree of migraine relief did not vary according to migraine subtype (Fig. 1). In follow-up, complete PFO closure (≤ 30 embolic tracks) was successfully achieved in 72% (36/50) of patients. Final closure status did not influence the degree of migraine relief. (chi-square test = 0.18, *p* = 0.91).

DISCUSSION

This study supports published findings that migraine headache in cryptogenic stroke patients with PFO is more prevalent (35%) than the presence of migraine headache in the general population (12%) (9). Similar to previously published reports of migraine relief after PFO closure (3-5), a significant reduction in overall frequency of migraine headaches was observed, with patients reporting on average an 80% reduction in monthly migraine events.

The significant treatment effect of transcatheter PFO closure on migraine frequency suggests the possibility of a common pathophysiologic substrate for selected patients with migraine and paradoxical embolism. This study is limited, however, by its nonrandomized, uncontrolled design, small sample size, and possibility of recall bias and placebo effect. Although the reported placebo effect in large, randomized trials of migraine prophylaxis (20% to 40%) (10) is significantly lower than the observed treatment effect (70%), it is possible the placement of an intracardiac device may have a more profound placebo effect than medical therapies.

Migraine relief was independent of the completeness of PFO closure, suggesting either a type II error due to insufficient sample-size, an effect based on partial "filtration" of microaggregates, or hypersensitivity of pm-TCD evaluation in quantifying residual shunt. It is possible that some

of the treatment effect could be due to aspirin therapy rather than PFO closure; however, this bias is debatable because 50% (25 of 50) of patients were taking aspirin before PFO closure, and the known effect of aspirin on migraine relief is modest (11). Although the effect of combination aspirin and clopidogrel therapy on migraine frequency has not been established, we observed sustained migraine relief after antiplatelet therapy was discontinued. The consistent observations of this and other studies are provocative and worthy of evaluation with a prospective, randomized trial using objective measures of migraine frequency and severity.

Reprint requests and correspondence: Dr. Jill Jesurum, 801 Broadway, Suite 927, Seattle, Washington 98104. E-mail: jill.jesurum@swedish.org.

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