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STRUCTURAL

Effect of Residual Interatrial Shunt on Migraine Burden After Transcatheter Closure of Patent Foramen Ovale

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ABSTRACT

OBJECTIVES This study sought to evaluate the long-term effect of transcatheter patent foramen ovale (PFO) closure on migraineurs with and without aura and examine the effect of residual right-to-left shunt.

BACKGROUND Many studies reported improvement in migraine symptoms after PFO closure, yet randomized trials failed to reach its clinical endpoints.

METHODS The study retrospectively analyzed data from 474 patients who underwent transcatheter PFO closure at Massachusetts General Hospital. Patients completed a migraine burden questionnaire at baseline and at follow-up. Migraine severity is reported as migraine frequency (days/month), average duration (min), and migraine burden (days × min/month). Improvement following closure was defined as complete abolishment of symptoms or >50% reduction in migraine burden.

RESULTS A total of 110 migraineurs who underwent PFO closure were included; 77.0% had aura and 23.0% were without aura, and 91.0% had a cryptogenic stroke. During long-term median follow-up of 3.2 (interquartile range: 2.1 to 4.9) years, there was a significant improvement in migraine symptoms in migraineurs with or without aura. Migraine burden was reduced by >50% in 87.0% of patients, and symptoms were completely abolished in 48%. Presence of aura was associated with abolishment of migraine (odds ratio: 4.30; 95% confidence interval: 1.50 to 12.30; $p = 0.006$). At 6 months after PFO closure, residual right-to-left shunt was present in 26% of patients. Absence of right-to-left shunt was associated with improvement in migraine burden by >50% (odds ratio: 4.60; 95% confidence interval: 1.30 to 16.10; $p = 0.017$).

CONCLUSIONS Long-term follow-up after transcatheter PFO closure was associated with significant improvement in migraine burden. Aura was a predictor of abolishing symptoms. Absence of residual right-to-left shunt was a predictor of significant reduction in migraine burden. (J Am Coll Cardiol Intv 2020;13:293–302) © 2020 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

OR = odds ratio

PFO = patent foramen ovale

TTE = transthoracic echocardiogram

The correlation between patent foramen ovale (PFO) and migraine type headaches has been well described in multiple studies (1–4). It is estimated that patients with PFO have 2- to 3-fold the expected prevalence of migraine compared with the general population (3,5). Migraineurs with PFO were found to be associated with the presence of aura, atrial septal aneurysm, and large right-to-left shunt (1,6–8).

The pathophysiological theory connecting PFO and migraines includes right-to-left shunt that permits paradoxical microemboli or shunting of humoral vasoactive factors that escape degradation in the pulmonary circulation (3,6,7).

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Multiple studies have reported improvement in migraine symptoms after transcatheter PFO closure (1,5,9–11), yet 3 randomized trials that followed patients for 6 to 12 months failed to reach their primary endpoints (12–14). Interestingly, in all of these randomized studies, there were subgroups demonstrating significant improvement in their migraine symptoms after device closure. To the best of our knowledge, none of these studies evaluated the role of residual right-to-left shunt on residual migraine symptoms.

In this paper, our objectives were to evaluate the long-term effect of transcatheter PFO closure on migraine frequency and burden and examine the association between residual right-to-left shunt and migraine burden.

METHODS

STUDY POPULATION. We retrospectively analyzed data from 474 consecutive patients who underwent transcatheter PFO closure at the Massachusetts General Hospital for cryptogenic stroke or for platypnea-orthodeoxia syndrome. Only patients with migraines and with long-term follow-up of ≥12 months were included in the study. The Massachusetts General Hospital Investigational Review Board approved the study. All patients agreed to participate in the study and gave written informed consent.

Platypnea-orthodeoxia was defined as breathlessness that is alleviated when lying down and exacerbated when sitting or standing up. Exercise-induced hypoxia was defined as an arterial O_2 saturation below 93% during cardiopulmonary exercise test.

Diagnosis of cryptogenic stroke was established when a PFO was demonstrated in the absence of other identifiable causes of a stroke. All patients underwent extensive evaluation to rule out other causes of systemic emboli in accordance with an established protocol agreed between cardiology, neurology, and hematology, and adjudicated by a committee with representatives from each discipline. Patient evaluation comprised a detailed neurological examination by a neurologist, computerized tomography imaging of the brain, carotid Doppler ultrasonography, cardiac magnetic resonance of the brain, 12-lead electrocardiogram, 2 to 4 weeks of cardiac event monitoring, 2-dimensional echocardiography (transthoracic echocardiogram [TTE] or transesophageal echocardiogram) with bubble study with and without the Valsalva maneuver, standard blood test and hypercoagulable work-up [protein C and S, antithrombin III, lupus anticoagulant, anticardiolipin antibodies, prothrombin gene mutation, lipoprotein(a), and factor V Leiden], Doppler of lower extremities, and pelvic magnetic resonance venous imaging to rule out deep vein thrombosis.

PFO CLOSURE. Using a transcatheter approach, a PFO closure was completed successfully in all patients. Closure was performed using either a CardioSEAL occluder device (NMT Medical, Boston, Massachusetts) or any of the Amplatzer PFO occluder, septal occluder, or Cribiform devices (Abbott Laboratories, Chicago, Illinois). The procedure was mostly performed under conscious sedation with few cases under general anesthesia. Patients were systemically anticoagulated with intravenous heparin (70 to 100 U/kg). All patients underwent diagnostic right heart catheterization before device implantation. PFO closure device was deployed under both fluoroscopic and echocardiographic guidance with either intracardiac echocardiography or transesophageal echocardiogram. Following device implantation, the presence of residual shunt was assessed by color flow Doppler and agitated saline administration. Routine TTE, chest x-ray, and 12-lead electrocardiogram were obtained 24 h after the procedure and before hospital discharge.

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Following the procedure, patients were treated with daily aspirin 325 mg for 6 months. Hypercoagulable patients were treated with warfarin for 3 additional months post-procedure.

OUTCOME. The primary outcome of interest was residual migraine symptoms, quantified as change in migraine severity and migraine improvement. Patients completed a standardized migraine burden questionnaire at baseline and at follow-up (Online Appendix). The questionnaire was designed in accordance with the guidelines of the International Headaches Society for migraineurs with or without aura (15).

Migraine severity was reported using 3 parameters: 1) migraine frequency, defined as the number of days with headache per month; 2) migraine duration, defined as the average duration of headache episodes in min; and 3) migraine burden, calculated as migraine frequency multiplied by the average duration of each episode (12). Migraine improvement following closure was defined as: 1) complete abolishment of symptoms; and 2) >50% reduction in migraine burden.

FOLLOW-UP. All patients underwent clinical follow-up and serial TTE at 1 day, and at 1, 6, and 12 months after device implantation and yearly thereafter for the next 5 years. Clinical follow-up data were obtained through periodic clinic visits, by phone calls using a standardized questionnaire for the assessment of migraine impact, and by review of electronic medical records. Echocardiography examinations were reviewed and assessed for the presence of residual shunts as previously reported (16). Residual right-to-left shunt was define as a positive bubble study on TTE at 6 months post-PFO closure. Mild shunt was defined as 1 to 10 bubbles appearing in the left atrium, moderate shunt as 11 to 30 bubbles, and large shunt as >30 bubbles appearing in the left atrium.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD and compared using Student's *t*-test, paired Student's *t*-test, or the Mann-Whitney *U* test, as appropriate. The distribution was confirmed by the Kolmogorov-Smirnov test. Categorical variables are presented as frequency and proportions and compared using chi-square or Fisher exact tests. To analyze the association of clinical characteristics with migraine symptom improvement after PFO closure, we performed univariate and multivariable logistic regression analysis with >50% reduction in migraine burden or complete abolishment of migraine symptoms as dependent variables and residual interatrial shunt, presence of aura, gender, age, and presence of atrial septum aneurysm as independent variables (selected a priori). We tested for interaction between covariates included in the multivariable regression model. Interaction terms were removed from the model if nonsignificant. All p values were 2-sided, and values <0.05 were considered statistically significant. All data were analyzed using SPSS version 20.0 (IBM Corporation, Armonk, New York).

TABLE 1 Baseline Characteristics

	All Patients (N = 110)	Migraine With Aura (n = 85)	Migraine Without Aura (n = 25)	p Value (± Aura)
Age, yrs	42.7 ± 11.5	41.5 ± 11.5	46.8 ± 10.5	0.042
Female	74 (67.3)	59 (69.4)	15 (60.0)	0.378
Hypertension	16 (14.5)	12 (14.3)	4 (16.0)	0.832
Diabetes	4 (3.7)	4 (4.8)	0 (0.0)	0.266
Caucasian	104 (94.5)	80 (94.1)	24 (96.0)	0.716
Hypercoagulability	23 (21.3)	19 (22.9)	4 (16.0)	0.461
History of smoking	41 (37.3)	33 (38.8)	8 (32.0)	0.535
Arrhythmias	8 (7.3)	7 (8.2)	1 (4.0)	0.473
Family history of migraines	44 (40.0)	35 (41.2)	9 (36.0)	0.636
Atrial septal aneurysm	30 (27.8)	23 (27.7)	7 (28.0)	0.977
Interatrial shunt at rest	69 (63.9)	53 (63.9)	16 (64.0)	0.989
Presenting symptoms				
CVA/TIA	100 (90.9)	77 (90.5)	23 (92.0)	0.736
Hypoxia	10 (9.1)	5 (9.4)	2 (8.0)	
Device type				
Amplatzer PFO occluder	38 (34.5)	30 (35.3)	8 (32.0)	0.813
Amplatzer Septal occluder	21 (19.1)	16 (18.8)	5 (20.0)	
Amplatzer Cribriform	12 (10.9)	8 (9.4)	4 (16.0)	
CardioSEAL	39 (35.5)	31 (36.5.0)	8 (32.0)	

Values are mean ± SD or n (%).
CVA = cerebrovascular accident; PFO = patent foramen ovale; TIA = transient ischemic attack.

RESULTS

We identified 110 patients with migraine-type headaches who underwent transcatheter PFO closure and who completed ≥12 months of follow-up. Eighty-five (77.0%) patients had a migraine with aura and 25 (23.0%) had a migraine without aura. Atrial septal aneurysm was found in 30 (28.0%) patients. Right-to-left shunt was noticed at rest in 69 (64.0%) patients. Degree of the shunt was mild in 75.0%, moderate in 21.0%, and large in 4.0%. Indications for PFO closure in our migraineur cohort included 100 (91.0%) patients with PFO-related neurological embolic events (84 stroke, 16 transient ischemic attack), and 10 (9.0%) patients with platypnea-orthodeoxia or exercise-induced hypoxia. Baseline demographics and PFO-related echocardiographic characteristics are summarized in Table 1. Apart from older age in

TABLE 2 Improvement in Migraine Symptom Metrics After PFO Closure

Metric	All Patients (N = 110)		Migraineurs With Aura (n = 85)		Migraineurs Without Aura (n = 25)		p Value (± Aura)
	Data	p Value	Data	p Value	Data	p Value	
Migraine frequency, days/month							
Before PFO closure	3.8 ± 5.7		4.1 ± 6.4		2.8 ± 2.5		0.323
After PFO closure	1.1 ± 3.2		1.1 ± 3.6		0.9 ± 1.2		0.722
Absolute change	-2.7 ± 6.1	<0.001	-2.9 ± 6.8	<0.001	-1.9 ± 2.6	0.001	0.456
Average migraine duration, min							
Before PFO closure	297 ± 267		308 ± 298		260 ± 107		0.437
After PFO closure	153 ± 296		143 ± 330		184 ± 129		0.545
Absolute change	-144 ± 150	<0.001	-164 ± 155	<0.001	-76 ± 111	0.002	0.009
Migraine burden (days × min/month)							
Before PFO closure	1,055 ± 1,508		1,117 ± 1,641		844 ± 922		0.428
After PFO closure	261 ± 602		278 ± 670		204 ± 270		0.591
Absolute change	-794 ± 1,410	<0.001	-839 ± 1,530	<0.001	-640 ± 899	0.002	0.419
Reduced migraine burden >50%	96 (87.3)		75 (88.2)		21 (84.0)		0.576
Migraine abolished	53 (48.2)		47 (55.3)		6 (24.0)		0.006

Values are mean ± SD or n (%).
PFO = patent foramen ovale.

patients without aura, there were no other significant differences in baseline characteristics between migraineurs with and without aura. PFO closure was successful in all patients. There was no difference in device type used between the groups (Table 1). All patients without indication for long-term anticoagulation were treated with daily aspirin 325 mg for 3 to 6 months following the procedure. Three patients were treated with dual antiplatelet therapy (aspirin 81 mg and clopidogrel 75 mg daily).

Baseline migraine symptoms for all patients and for those with and without aura are shown in Table 2. Twenty-one of the 110 (19.0%) migraineurs did not complete the migraine severity questionnaire before the PFO closure procedure and filled it retrospectively. There were no significant differences in baseline frequency, duration, or burden of migraine between the groups (baseline migraine burden 1,117 vs. 844 days × min/month; p = 0.42).

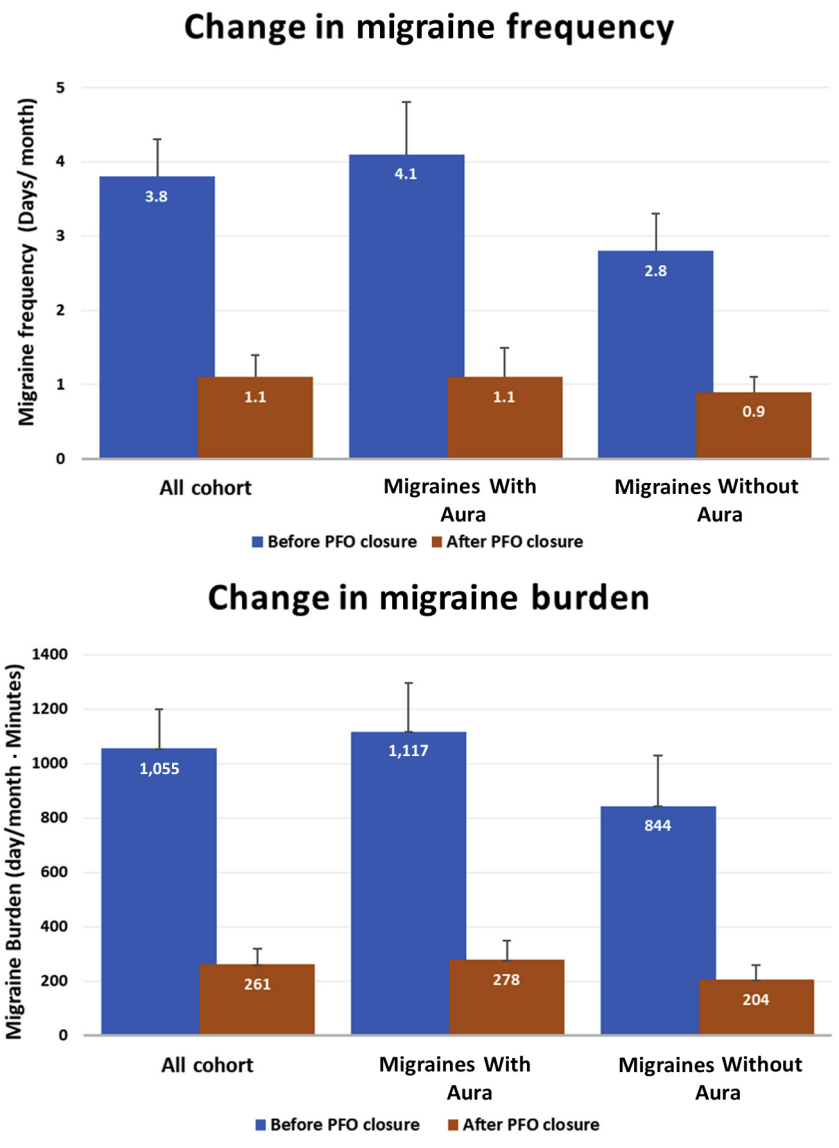
Periprocedural complications included 1 (0.9%) patient with pericardial effusion, 2 (1.8%) patients with atrial fibrillation, and 1 (0.9%) patient with device embolization. There were no periprocedural deaths. During the study follow-up, 2 (1.8%) patients had recurrent stroke and 1 (0.9%) patient had recurrent transient ischemic attack. Four (3.6%) patients underwent repeat procedure due to persistence of significant interatrial shunt.

During median follow-up of 3.2 (interquartile range: 2.1 to 4.9) years after PFO closure, there was a significant decrease in all symptom criteria for the overall migraineurs population (Figure 1). In our cohort, 96 (87.0%) patients had reduced their migraine burden by >50% and 53 (48.0%) patients had abolished their migraine symptoms (Table 2). Four (3.6%) patients had reported worsening of migraine symptoms. Importantly, migraine burden and frequency decreased equally in migraineurs with and without aura (Central Illustration, Table 2). Moreover, a significant reduction in all symptoms criteria was noticed even in patients who did not abolish their migraines (n = 57). Migraine frequency reduced from 4.9 ± 6.7 days/month to 2.1 ± 4.3 days/month (p = 0.006), episode duration reduced from 322 ± 355 min to 294 ± 359 min (p = 0.001), and migraine burden reduced from 1,409 ± 1,927 days × min/month to 504 ± 763 days × min/month (p < 0.001).

There was no significant difference in the proportion of patients with or without aura who achieved >50% reduction in their migraine burden (88.2% vs. 84.0%; p = 0.57). However, migraine abolition occurred more frequently in migraineurs with aura (55.0% vs. 24.0%; unadjusted odds ratio [OR]: 3.90; 95% confidence interval [CI]: 1.40 to 10.70; p = 0.006) (Central Illustration, Table 3). In multivariable logistic regression analysis, after adjusting for clinically relevant covariates (age, gender, absence of residual shunt, and atrial septal aneurysm), presence of aura was independently associated with abolishment of migraine (adjusted OR: 4.30; 95% CI: 1.50 to 12.30; p = 0.006) (Table 3).

At 6 months after PFO closure, residual right-to-left shunt of any severity was found in 29 (26.0%) patients (mild right-to-left shunt was detected in

FIGURE 1 **Change in Migraine Frequency and Burden After Transcatheter PFO Closure**

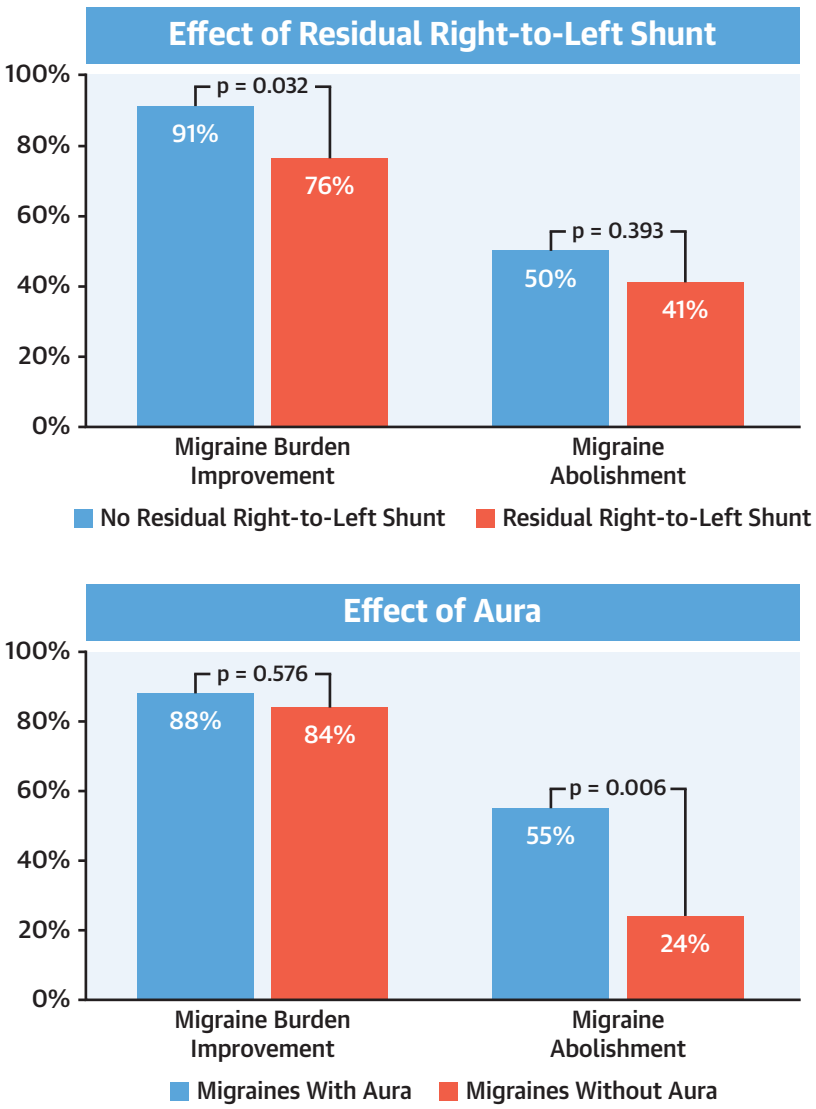


Improvement in migraine frequency **(upper)** and migraine burden **(lower)** at 3.2 years after patent foramen ovale (PFO) closure. Migraine burden and frequency decreased significantly in both migraineurs with and without aura. **Error bars** represent SEM.

18.0%, moderate in 7.0%, and large in 1.0%). "Effective" closure, a term defined in stroke preventing studies (17) and including procedures resulting with none or mild residual interatrial shunt, was reached in 92.0%. Rates of residual right-to-left shunt were similar between migraineurs with or without aura (26.0% vs. 28.0%; p = 0.83). As expected, the rate of early post-procedural right-to-left shunt noticed in the first 24 h post-procedure was higher than the residual right-to-left shunt noticed at 6 months (52.0% vs. 26.0%). The majority (65.0%) of the acute post-procedure residual shunts were trace or mild shunt.

Absence of right-to-left shunt at 6 months was more common in patients who had >50% reduction in migraine burden (77.0% vs. 23.0%; unadjusted OR: 3.36; 95% CI: 1.10 to 10.60; p = 0.032) (**Table 3**, Online Table 1). Absence of residual right-to-left

CENTRAL ILLUSTRATION **Characterization of Patients With Migraine Improvement After Transcatheter PFO Closure**



Ben-Assa, E. et al. J Am Coll Cardiol Intv. 2020;13(3):293–302.

At 3.2 years after patent foramen ovale (PFO) closure, 87.0% of our cohort reduced their migraine burden by >50% and 48.0% abolished their migraine symptoms. Absences of residual right-to-left shunt at 6 months post-PFO closure was more frequently found in patients with >50% migraine burden reduction **(upper)** and migraine abolition occurred more frequently in migraineurs with aura **(lower)**.

shunt was identified as an independent predictor of >50% reduction in migraine burden in multivariable analysis after adjusting for clinically relevant covariates (age, gender, presence of aura, and atrial septal aneurysm) (adjusted OR: 4.60; 95% CI: 1.30 to 16.10; p = 0.017). Absence of residual shunt was associated with >50% reduction in migraine burden in both patients with and without aura (p for interaction >0.05).

DISCUSSION

The association between PFO and migraine type headache is fairly complex (2,18,19). There are PFO patients without migraines and there are migraineurs without PFO. Nevertheless, the symptomatic improvement in migraineurs post-PFO closure seen in nonrandomized studies (1,5,9–11) was not reproducible in randomized trials with relatively short-

term follow-up (12–14). Currently, we are left with conflicting data to provide to our patients who suffer from migraines and seek ways to relieve it.

Our study adds another layer of information and a new perspective on the relationship of PFO and migraine. In our cohort, at long-term median follow-up of 3.2 (interquartile range: 2.1 to 4.9) years after PFO closure, we demonstrate that: 1) ~90% of patients improved their migraine burden by >50% irrespective of the presence of aura and ~50% completely abolished their migraine symptoms; 2) presence of aura was a significant predictor of complete abolishment of migraine symptoms following PFO closure; and 3) absence of residual right-to-left shunt at 6 months post-PFO closure was an independent predictor of >50% reduction in migraine burden.

The previous 3 largest randomized studies (12–14) have taught us abundantly regarding the intricate relationship between migraine headache and PFO. The MIST (Migraine Intervention With STARFlex Technology) study (12) was a sham-controlled trial whose primary endpoint of migraine abolishment in 6 months was not achieved, yet an exploratory analysis showed significant reduction in migraine frequency (days/month) in the PFO closure group ($p = 0.027$). The PRIMA (Percutaneous Closure of PFO in Migraine with Aura) study (13) was not a sham-controlled study and was terminated prematurely due to low enrollment, it analyzed 107 patients for primary endpoint of reduction in migraine monthly frequency at 9 to 12 months. Although primary endpoint was not significant, multiple secondary endpoint were in favor of PFO closure showing >50% reduction in migraine frequency ($p = 0.02$) as well as markedly improvement ($p = 0.01$) and significant rates of abolishment in migraines with aura ($p < 0.005$). Last, the PRIMIUM (Percutaneous Closure of Patent Foramen Ovale in Patients With Migraine) study (14) that was sham controlled and needed 7 years of recruitment to complete, as it targeted even more severe and refractory migraineurs population. Again, the primary endpoint of >50% reduction in migraine attacks was not reached in the whole cohort yet was achieved in migraineurs with aura ($p = 0.015$). Moreover, a significant reduction in monthly headache frequency ($p = 0.025$) and higher rates of migraine abolishment ($p = 0.01$) were reported.

In summary, each study had different inclusion criteria and different primary endpoints. All primary endpoints demonstrated numerically yet nonsignificant benefit of PFO closure. Importantly, many secondary clinically relevant endpoints were significant in favor of closure, specifically in migraineurs with aura. It is important to notice that all 3 studies targeted highly symptomatic and refractory migraineurs, had difficulties in recruitment, and had relatively short follow-up period of no more than 1 year. Interestingly, none of the studies analyzed the impact of residual right-to-left shunt on symptomatic relief and only some reported its prevalence.

TABLE 3 Predictors of Migraine Burden Improvement and Migraine Abolishment

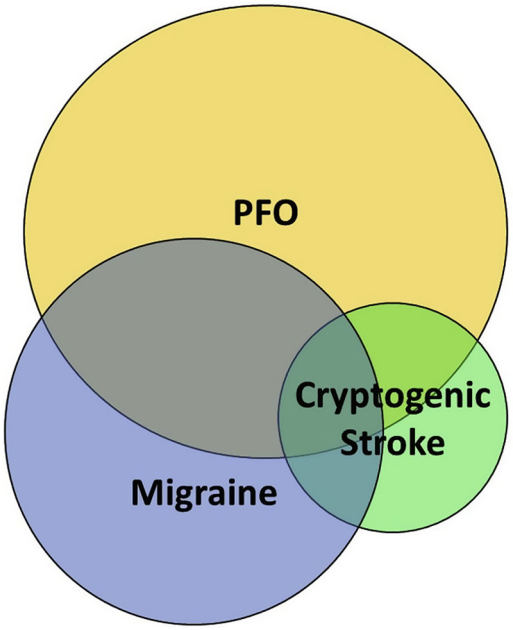
	Univariate Analysis			Multivariable Analysis		
	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
>50% improvement in migraine burden						
Absence of residual shunt*	3.36	1.06–10.60	0.039	4.61	1.32–16.10	0.017
Aura	1.43	0.40–5.02	0.58	1.31	0.35–4.90	0.66
Gender	0.52	0.13–1.99	0.34	0.49	0.12–1.90	0.29
Age	0.98	0.93–1.02	0.32	0.97	0.92–1.02	0.13
Atrial septum aneurysm	5.35	0.66–42.80	0.11	8.34	0.96–72.40	0.054
Abolishment of migraines						
Absence of residual shunt*	1.45	0.61–3.42	0.39	1.36	0.55–3.35	0.50
Aura	3.92	1.42–10.78	0.008	4.34	1.53–12.3	0.006
Gender	0.76	0.34–1.69	0.50	0.70	0.30–1.64	0.42
Age	1.01	0.97–1.04	0.72	1.01	0.97–1.05	0.51
Atrial septum aneurysm	0.83	0.35–1.95	0.67	0.80	0.32–1.97	0.62

*Residual interatrial right-to-left shunt at 6 months post-patent foramen ovale closure.
CI = confidence interval.

Several aspects of our study are novel and should be emphasized. First, we used a migraine burden scale to evaluate change in symptoms, a metric that incorporates both frequency and duration of migraine, and better represents the impact of symptoms on our patients. Second, we emphasized the importance of long-term follow-up after PFO closure that enabled us to demonstrate significant improvement in migraine symptoms in the majority of patients irrespective of the presence of aura. Third, the presence of aura correlated with complete abolishment of migraine symptoms. Last, and most important, the absence of residual right-to-left shunt at 6 months after PFO closure correlated with significant reduction in migraine burden.

Patients with PFO with large right-to-left shunt have higher association with migraines compared with those with small shunts (5,7,12), a finding that might suggest a dose-effect relationship between interatrial shunt and migraine symptoms. Nevertheless, the pathophysiology underlying migraine and right-to-left shunting is only partially understood. Several theories were suggested and probably contribute together to the variability of this association. First, right-to-left shunt may allow vasoactive, migraine-provoking metabolites to bypass the pulmonary filter and reach the cerebral circulation (3,20).

FIGURE 2 Overlapping Clinical Presentation of PFO, Cryptogenic Stroke, and Migraine Headache



The clinical presentations of patent foramen ovale (PFO), cryptogenic stroke, and migraine headaches may be considered as a Venn diagram of overlapping **circles**. Each clinical syndrome exists without the other, as well as overlaps separately or commonly with the other entities. The **circles** are scaled to approximately represent the overlap of the various entities based on published data.

One such vasoactive substance is that has been implicated in migraine attacks is serotonin, and its metabolism involves degradation through lung monoamine oxidase (21). Interestingly, it has been found that plasma levels of serotonin decrease after percutaneous closure of PFO (22). Another mechanism that may contribute to the pathogenesis of right-to-left shunting and migraines, specifically in migraineurs with aura, is paradoxical microembolism (7,18). This can trigger focal transient cerebral ischemia, which is believed to be the electrophysiological substrate of aura (19). Importantly, paradoxical embolism through PFO appears to be more frequent in the posterior circulation, the same area that is involved in hypoperfusion during the visual aura (6). Antiplatelet drugs might prevent microemboli development as well as reduce the release of serotonin that can contribute to platelets aggregation. The findings that aspirin has a significant prophylactic effect on migraine (23) and clopidogrel reduces migraine attack frequency after transcatheter closure of PFO (24) strengthen these theories. Furthermore, PFO has been linked to some degree of arterial blood oxygen desaturation. Hypoxia may directly induce aura, as well as increase the likelihood of paradoxical microembolism through induced expression of plasminogen activator inhibitor-1 (20).

Our finding that successful complete PFO closure without residual shunt at 6 months is significantly associated with >50% reduction in migraine burden strengthens these pathophysiological theories. It allows us to understand the possible underlying mechanism and explain this phenomenon to our patients. This finding may also explain the variability in symptomatic relief noticed in previous studies. Whereas "effective closure" of PFO that permits mild residual shunt (17) might be sufficient to reduce the risk of cryptogenic stroke, mild residual shunts may still allow vasoactive metabolites and microemboli to cross over and to cause migraine.

Learning from previous studies and from the data we present here, our group believes that future randomized studies should be meticulously planned to better characterize the subpopulations of migraineurs that will benefit from PFO closure. Investigator may consider including not only the refractory migraineurs populations, consider less stringent primary endpoints, and consider follow-up patients for longer periods. Regarding efficacy of device closure, we recommend evaluating residual right-to-left shunt at 6 to 12 months post-closure and considering including residual shunt analysis in the outcome metrics, as well as evaluating the role of "complete" versus "effective" closure.

As previously described by others, our multidisciplinary cardio-neuro-hematology team believes that the clinical presentations of PFO, stroke, and migraine headaches should be considered as a Venn diagram of overlapping circles (**Figure 2**). Each of these clinical entities has a wide spectrum of presentation and pathophysiology. Each clinical syndrome exists without the other, as well as overlap separately or commonly with the other entities. This paradigm may explain the variability in migraineurs response to PFO closure as well as enable us to target specific populations that might have higher chance to benefit from closure. Moreover, we can speculate that migraine symptoms that are not improving after successful PFO closure may be related to other migraine pathophysiological mechanisms that are not related to right-to-left shunting.

STUDY LIMITATIONS. First, we studied a specific patient population that had a combination of PFO, cryptogenic stroke, and migraine. Therefore, our results may not be generalizable to all patients with

migraines. Nevertheless, as we described previously, we believe that there is a unique relationship among presence of PFO, history of stroke, and history of migraines. It might well be that this specific population is the one that will most benefit from PFO closure in terms of migraine symptom reduction. Second, this is a retrospective observational study, and may introduce bias to our analysis, specifically recall bias, as 19.0% of our cohort did not complete the migraine burden questionnaire pre-procedurally and instead completed it retrospectively. Nevertheless, our procedural data was obtained from a prospective registry that maintained a high level of data recruiting. Third, we performed analysis of residual shunt at 6-month post-PFO and correlated it with long term symptomatic improvement. We hypothesized that after 6 months, further device endothelialization will not occur; hence, this time point may predict long-term migraine symptoms improvement. It is important to mention that patterns of device endothelialization have not been studied well and although some studies show complete endothelization at 12 weeks post-procedure, others demonstrated that specific devices may have incomplete endothelialization even years after deployment. Last, we were not able to evaluate the effect of different antiplatelet regiments on migraine symptoms. Several studies have reported the beneficial effect of clopidogrel on migraine symptoms (25). Nevertheless, all of our patients were on aspirin after closure and only 3 were treated with additional clopidogrel. However, this did make our cohort homogenous, allowing us to specifically examine the effect of residual shunt.

CONCLUSIONS

Long-term follow-up after transcatheter PFO closure in patients with cryptogenic stroke and migraine headaches resulted in significant improvement in migraine symptom burden in the majority of patients. Almost 50% of patients completely abolished their migraine symptoms, and the presence of aura was a significant predictor of such symptomatic resolution. The absence of residual shunt at 6 months post-closure was an independent predictor of reduction in migraine burden. Larger and dedicated randomized trials that will include different populations of migraineurs with and without stroke and will evaluate long-term improvement in symptoms after PFO closure are needed to fully appreciate the complexity of these overlapping syndromes.

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PERSPECTIVES

WHAT IS KNOWN? The correlation between PFO and migraine-type headaches has been well described. The benefit of transcatheter PFO closure in reducing migraine symptoms has showed conflicting results.

WHAT IS NEW? At 3.2 years after PFO closure, migraine symptoms improved in the majority of our cohort, both in migraineurs with and without aura. Absence of residual interatrial shunt was associated with significant reduction in migraine burden and presence of aura was associated with abolishment of symptoms.

WHAT IS NEXT? New randomized trials are currently under design to identify specific migraineur subpopulations that may benefit from PFO closure.

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KEY WORDS migraine, patent foramen ovale, right-to-left shunt

APPENDIX For an expanded Methods section and a supplemental table, please see the online version of this paper.