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Effect of residual interatrial shunt on migraine burden after transcatheter closure...

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

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Abstract

Objectives: To evaluate the long-term effect of transcatheter patent foramen ovale (PFO) closure on migraineurs with and without aura, and to 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: We 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 (minutes), and migraine burden (days*minutes/month). Improvement following closure was defined as complete abolishment of symptoms or > 50% reduction in migraine burden.

Results: 110 migraineurs who underwent PFO closure were included. 77% had aura and 23% without aura. 91% had a cryptogenic stroke. During long-term median follow-up of 3.2 (IQR 2.1- 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% of patients, and symptoms were completely abolished in 48%. Presence of aura was associated with abolishment of migraine (OR 4.3 [95% CI 1.5-12.3]; 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% (OR 4.6 [95% CI 1.3-16.1]; p=0.017).

Conclusions: Long-term follow up after transcatheter PFO closure was associated with significant improvement in migraine burdeiguren. Aura was a predictor of abolishing symptoms.

Absence of residual right-to-left shunt was a predictor of significant reduction in migraine burden.

Key Words: Patent Foramen Ovale; Migraine; Right to left shunt

Condensed Abstract: The association between PFO and migraine type headache is well established. Data regarding the benefit of transcatheter PFO closure in reducing migraine symptoms are conflicting. We have followed 110 migraineurs patients for 3.2 years after PFO closure and demonstrated a significant improvement in migraine symptoms. Notably, the presence of aura was a predictor of abolishing symptoms, and absence of residual right-to-left shunt was a predictor of significant reduction in migraine burden. This novel insight regarding the pathophysiology of PFO and migraines may assist in characterizing the migraineurs subpopulation that will likely benefit from PFO closure.

Abbreviation list: PFO=Patent Foramen Ovale; TTE = Trans-thoracic echocardiogram; TEE= Trans-esophageal echocardiogram.

Introduction

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 2-3 fold the expected prevalence of migraine compared to 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 and/or shunting of humoral vasoactive factors that escape degradation in the pulmonary circulation (3, 6, 7).

Multiple studies have reported improvement in migraine symptoms after transcatheter PFO closure (1, 5, 9–11), yet three randomized trials that followed patients for 6-12 month, failed to reach their primary endpoints (12–14). Interestingly in all of these randomized studies there were sub-groups 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 to 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 (MGH) 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 MGH 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 O2 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 (CT) imaging of the brain, carotid doppler ultrasonography, magnetic resonance imaging (MRI) of the brain, 12-lead electrocardiogram (ECG), 2-4 weeks of cardiac event monitoring, 2-D echocardiography (transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE) with bubble study with and without the Valsalva maneuver, standard blood test and hypercoagulable work-up (protein C and S, anti-thrombin III, lupus anticoagulant, anti-cardiolipin 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, Inc) or any of the Amplatzer PFO occluder, septal occluder or Cribiform devices (Abbott medical). The procedure was mostly performed under conscious sedation with few cases under general anesthesia. Patients were systemically anticoagulated with intravenous heparin (70-100 Units/kg). All patients underwent diagnostic right heart catheterization prior to device implantation. PFO closure device was deployed under both fluoroscopic and echocardiographic guidance with either intracardiac echocardiography (ICE) or TEE. 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 ECG were obtained 24 hours after the procedure and before hospital discharge. Following the procedure, patients were treated with daily aspirin 325 mg for six 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 (Supplemental material). 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: A) migraine frequency, defined as the number of days with headache per month. B) migraine duration, defined as the average duration of headache episodes in minutes. C) migraine burden, calculated as migraine frequency multiplied by the average duration of each episode (12). Migraine improvement following closure was defined as: A) complete abolishment of symptoms; B) >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 five 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 trans-thoracic echocardiogram at 6 months post PFO closure. Mild shunt was defined as 1-10 bubbles appearing in the left atrium, moderate shunt as 11-30 bubbles and large shunt as >30 bubbles appearing in the left atrium.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation and compared using Student's t-test, paired 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 percentages (%) and compared using Chi-square or Fisher’s 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, presence of atrial septum aneurysm and 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 non-significant. All p values were 2-sided, and values <0.05 were considered statistically significant. All data were analyzed using SPSS, Version 20.0 (IBM Corp., Armonk, NY).

Results

We identified 110 patients with migraine type headaches who underwent transcatheter PFO closure and who completed ≥12 months follow-up. Eighty-five (77%) patients had aura and 25 (23%) had migraine without aura. Atrial septal aneurysm was found in 30 (28%) patients. Right to left shunt was noticed at rest in 69 (64%) patients. Degree of the shunt was mild in 75%, moderate in 21% and large in 4%. Indications for PFO closure in our migraineurs cohort included 100 patients (91%) with PFO-related neurological embolic events (stroke: n=84, TIA: n=16), and 10 patients (9%) with platypnea-orthodeoxia or exercise-induced hypoxia. Baseline demographics and PFO related echocardiographic characteristics are summarized in **Table 1**. Apart from older age in 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 patient without indication for long term anticoagulation were treated with daily aspirin 325 mg for 3-6 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 migraineurs (19%) 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 day/month*minutes; p= 0.42).

Peri procedural complications included 1 patient (0.9%) with pericardial effusion, 2 patients (1.8%) with atrial fibrillation and 1 patient (0.9%) with device embolization. There was no periprocedural death. During the study follow up 2 patients (1.8%) had recurrent stroke and 1

patient (0.9%) had recurrent TIA. Four patients (3.6%) underwent repeat procedure due to persistence of significant interatrial shunt.

During median follow-up of 3.2 (IQR 2.1- 4.9) years after PFO closure, there was a significant decrease in all symptom criteria for the overall migraineurs population. In our cohort, 96 patients (87%) had reduced their migraine burden by >50% and 53 patients (48%) had abolished their migraine symptoms (**Table 2**). Four patients (3.6%) 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 to 2.1±4.3 days/month (p=0.006), Episode duration reduced from 322±355 to 294±359 minutes (p=0.001), and migraine burden reduced from 1409±1927 to 504±763 day/month*minutes (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%; p=0.57). However, migraine abolition occurred more frequently in migraineurs with aura (55% vs. 24%; unadjusted OR 3.9 [95% CI 1.4-10.7]; 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 4.3 [95% CI 1.5-12.3]; p=0.006) (**Table 3**).

At 6 months after PFO closure, residual right-to-left shunt of any severity was found in 29 (26%) patients (mild right to left shunt was detected in 18%, moderate in 7% and large in 1%). “Effective” closure, a term defined in stroke preventing studies (24) and includes procedures resulting with none or mild residual interatrial shunt, was reached in 92%. Rates of

residual right to left shunt were similar between migraineurs with or without aura (26% vs. 28%, respectively, p=0.83). As expected, the rate of acute post procedural right-to-left shunt imaged in the first 24 hours post procedure was higher than the residual right-to-left shunt noticed at 6 months (52% vs. 26 %). The majority (65%) of the acute post procedure residual shunts were trace/mild shunt.

Absence of right-to-left shunt at 6 months was more common in patients who had >50% reduction in migraine burden (77% vs 23%, unadjusted OR 3.36 [95% CI 1.1-10.6]; p=0.032) (**Table 3, Supplemental table**). Absence of residual right-to-left 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 4.6 [95% CI 1.3-16.1]; 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, 17, 18). There are PFO patients without migraines and there are migraineurs without PFO. Nevertheless, the symptomatic improvement in migraineurs post PFO closure seen in non-randomized 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 (IQR 2.1-4.9) years after PFO closure, we demonstrate that: (i) ≈90% of patients improved their migraine burden by >50% irrespective of the presence of aura, and ≈50% completely abolished their migraine symptoms, (ii) presence of aura was a significant predictor of complete abolishment of migraine symptoms following PFO closure, and (iii) 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 study (12) was a sham-controlled trial whos 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 (13) study 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 9-12 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). Lastly the PRIMIUM study (14) that was sham controlled, 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 non-significant 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 a highly symptomatic and refractory migraineurs patients, all had difficulties in recruitment and all 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.

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. Lastly, and most importantly, 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 to 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, 19). One such vasoactive substance is that has been implicated in migraine attacks is serotonin, and its metabolism involves degradation through lung monoamine oxidase (20). Interestingly, it has been found that plasma levels of serotonin decrease after percutaneous closure of PFO (21). Another mechanism that may contribute to the pathogenesis of right-to-left shunting and migraines, specifically in migraineurs with aura, is paradoxical micro-embolism (7, 17). 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). Anti-platelet drugs might prevent microemboli development as well as reduce the release of serotonin that can contribute to platelets aggregation. The finding that aspirin has a significant prophylactic effect on migraine (22), and clopidogrel reduces migraine attack frequency after transcatheter closure of PFO (23) 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-1 (19).

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 to 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 (24) might be sufficient to reduce the risk of cryptogenic stroke, mild residual shunts may still allow vasoactive metabolites as well as micro-emboli 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 in order 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 to follow up patients for longer periods. Regarding efficacy of device closure, we recommend evaluating residual right to left shunt at 6-12 months post closure and to consider including residual shunt analysis in the outcome metrics, as well as evaluating the role of "complete" vs. "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 mechanism that are not related to right-to-left shunting.

Our study has certain 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 patient with migraines. Nevertheless, as we described above, we believe that there is a unique relationship between 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, and specifically recall bias as 19% of our cohort did not complete the migraine burden questionnaire pre procedurally, and 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 has not been studied well in the literature and while some studies show complete endothelization at 12 weeks post procedure, other demonstrated that specific devices may have incomplete endothelialization even years after deployment. Lastly, 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. This did however, make our cohort homogenous allowing us to specifically examine the effect of residual shunt.

In conclusion, 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 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.

Perspective:

What is Known?

- The correlation between patent foramen ovale (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 following 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 migraineurs subpopulations that may benefit from PFO closure

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Figure Titles and Legends:

Figure 1 - Change in migraine frequency and burden after transcatheter PFO closure

Improvement in migraine frequency (upper panel) and migraine burden (lower panel) at 3.2 years after PFO closure. Migraine burden and frequency decreased significantly in both migraineurs with and without aura (Error bars represents standard error).

Central Illustration – Characterization of patients with migraine improvement after transcatheter PFO closure

At 3.2 years after PFO closure, 87% of our cohort reduced their migraine burden by >50% and 48% 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 panel) and migraine abolition occurred more frequently in migraineurs with aura (lower panel).

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 overlap separately or commonly with the other entities. The circles are scaled to approximately represent the overlap of the various entities based on published literature.

Table 1 – Baseline characteristics

	All cohort (n=110)	Migraine with Aura (n=85)	Migraine without Aura (n=25)	P value (+/- Aura)
Age	42.7 ± 11.5	41.5 ± 11.5	46.8 ± 10.5	**0.042**
Gender (female)	74 (67.3)	59 (69.4)	15 (60)	0.378
Hypertension	16 (14.5)	12 (14.3)	4(16)	0.832
Diabetes	4 (3.7)	4 (4.8)	0 (0)	0.266
Caucasian	104 (94.5)	80 (94.1)	24 (96)	0.716
Hypercoagulability	23 (21.3)	19 (22.9)	4 (16)	0.461
History of smoking	41 (37.3)	33 (38.8)	8 (32)	0.535
Arrhythmias	8 (7.3)	7 (8.2)	1 (4)	0.473
Family History of migraines	44 (40)	35 (41.2)	9 (36)	0.636
Atrial septal aneurysm	30 (27.8)	23 (27.7)	7 (28)	0.977
Interatrial shunt at rest	69 (63.9)	53 (63.9)	16 (64)	0.989
Presenting symptoms				
CVA/TIA	100 (90.9)	77 (90.5)	23 (92)	0.736
Hypoxia	10 (9.1)	5 (9.4)	2(8)	
Device Type				
Amplatzer PFO occluder	38 (34.5)	30 (35.3)	8 (32)	0.813
Amplatzer Septal occluder	21 (19.1)	16 (18.8)	5 (20)	
Amplatzer Cribriform	12 (10.9)	8 (9.4)	4 (16)	
CardioSEAL	39 (35.5)	31 (36.5)	8 (32)	

Data presented as mean +/- standard deviation, or n (%)

Table 2 – Improvement in migraine symptom metrics after PFO closure

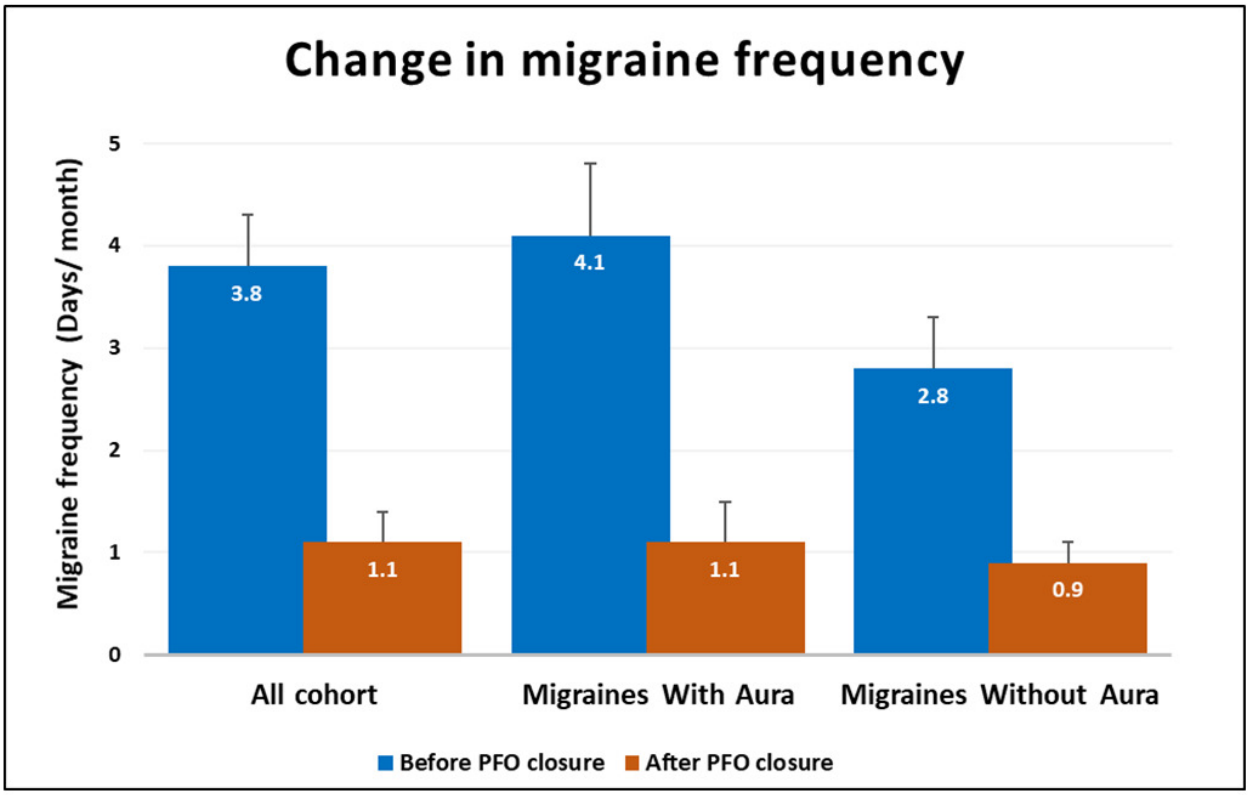
		All cohort (n=110)		Migraines With Aura (n=85)		Migraines Without Aura (n=25)		P value (+/- Aura)
Migraine frequency (Days/ month)	**Before PFO closure**	3.8 ± 5.7		4.1 ± 6.4		2.8 ± 2.5		0.323
	After PFO closure	1.1 ± 3.2		1.1 ± 3.6		0.9± 1.2		0.722
	Absolute Change	-2.7 ± 6.1	**P<0.001**	-2.9 ± 6.8	**P<0.001**	-1.9 ± 2.6	**P=0.001**	0.456
Average migraine duration (Minutes)	**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	**P<0.001**	-164 ± 155	**P<0.001**	-76 ± 111	**P=0.002**	**0.009**
Migraine burden (day/month * Minutes)	**Before PFO closure**	1055 ± 1508		1117 ± 1641		844 ± 922		0.428
	After PFO closure	261 ± 602		278 ± 670		204 ± 270		0.591
	Absolute Change	-794 ± 1410	**P<0.001**	-839 ± 1530	**P<0.001**	-640 ± 899	**P=0.002**	0.419
Reduced migraine burden >50%		96 (87.3%)		75 (88.2%)		21 (84%)		0.576
Migraine abolished		53 (48.2%)		47 (55.3%)		6 (24%)		**0.006**

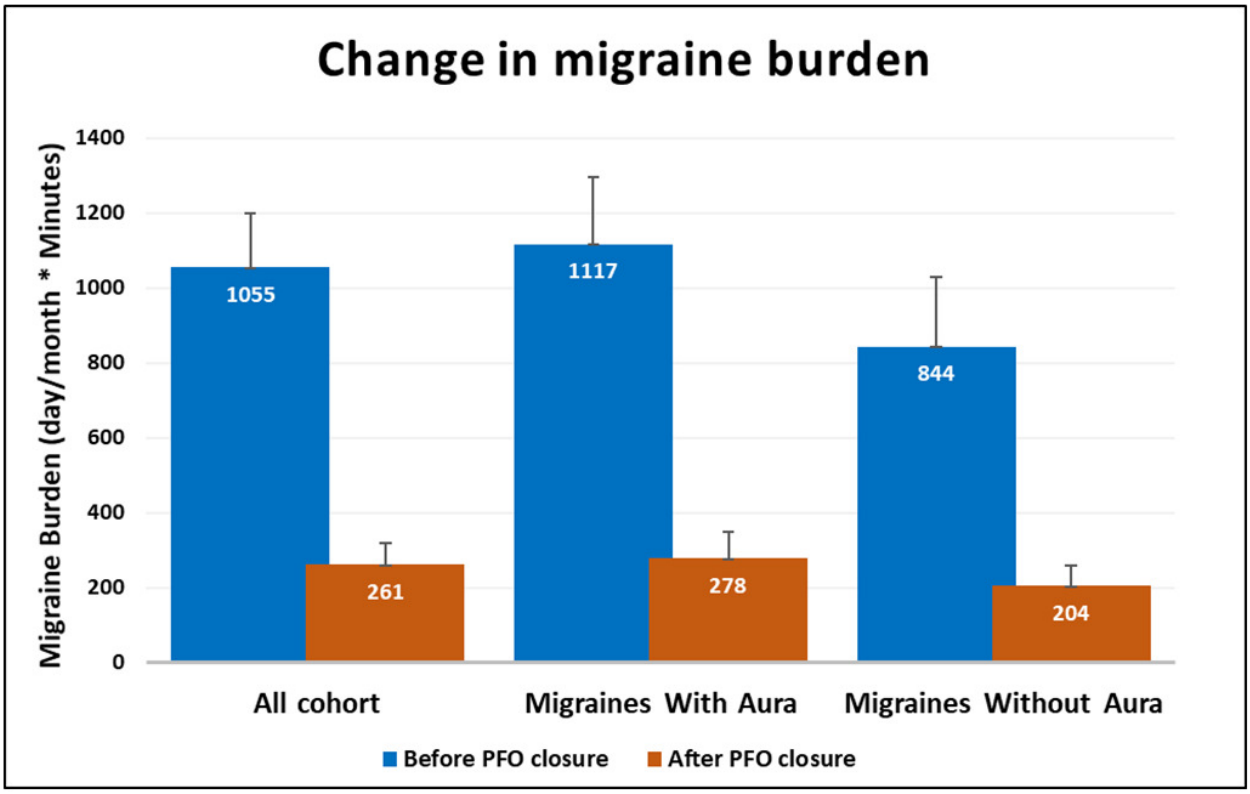
Data presented as mean +/- standard deviation

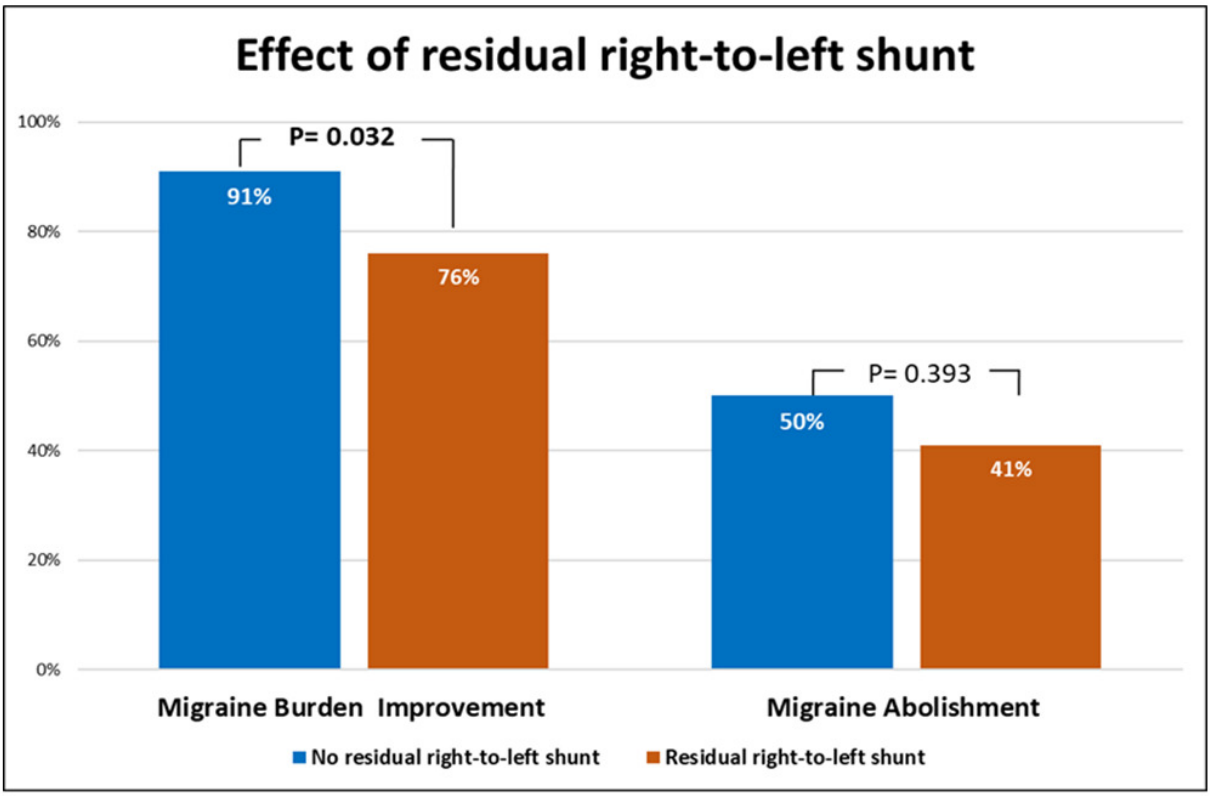
Table 3 – Predictors of migraine burden improvement and migraine abolishment.

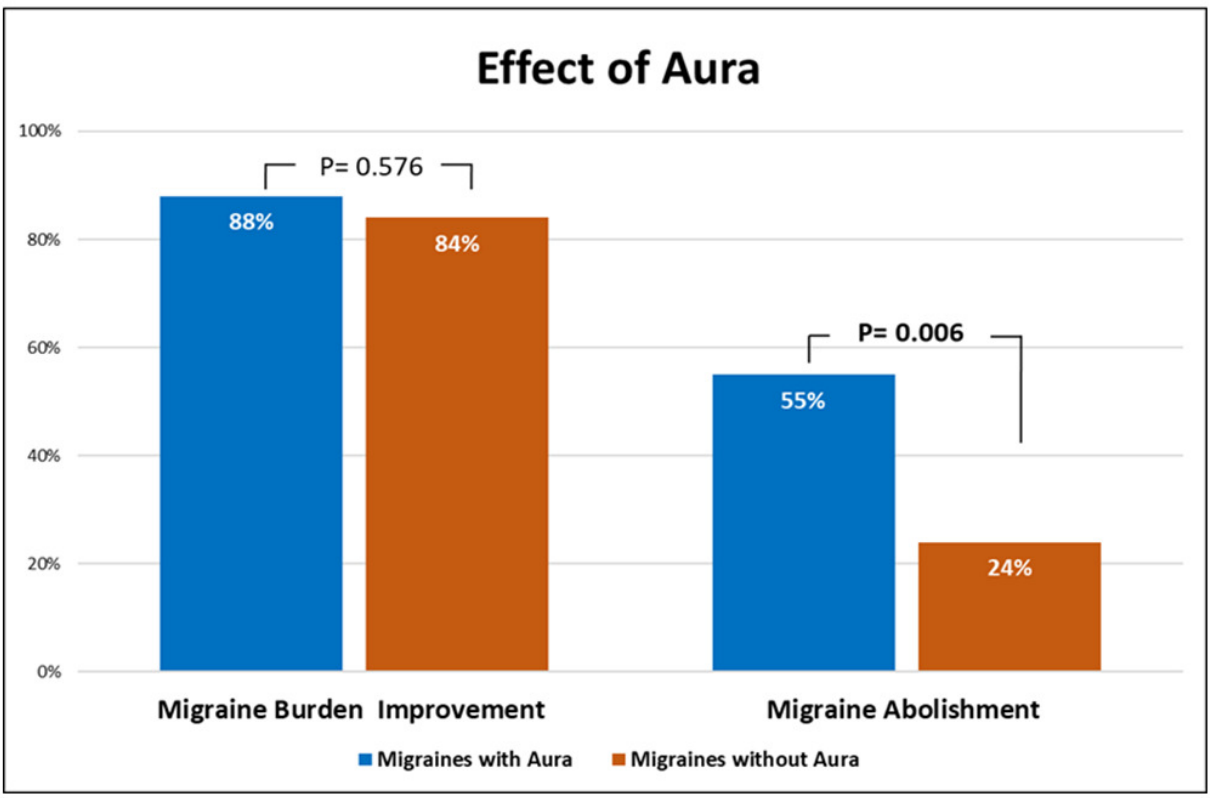
	Univariate analysis			Multivariable analysis		
	Odds ratio	**95% CI**	**P value**	**Odds ratio**	**95% CI**	**P value**
Greater than 50% Improvement in migraine burden						
Absence of Residual Shunt*	3.36	1.06 – 10.6	**0.039**	4.61	1.32 - 16.1	**0.017**
Aura	1.43	0.40 - 5.02	0.58	1.31	0.35 - 4.9	0.66
Gender	0.52	0.13 - 1.99	0.34	0.49	0.12 - 1.9	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 – 42.8	0.11	8.34	0.96 – 72.4	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

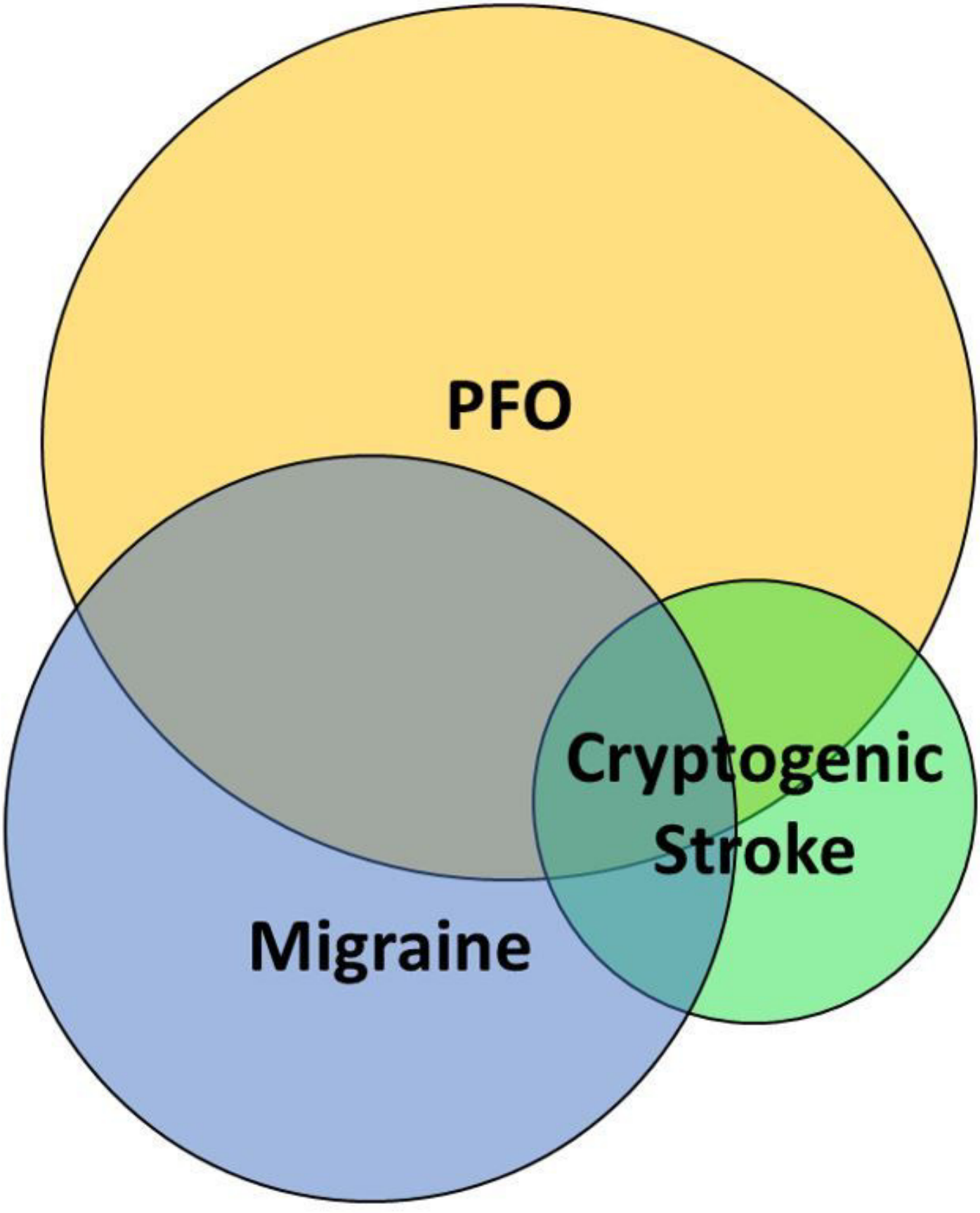
* Residual interatrial right-to-left shunt at 6 month post PFO closure


Change in migraine frequency
Migraine frequency (Days/ month)
5
4
3
2
1
0
3.8
1.1
4.1
1.1
2.8
0.9
All cohort
Migraines With Aura
Migraines Without Aura
Before PFO closure
After PFO closure


Change in migraine burden
Migraine Burden (day/month * Minutes)
1400
1200
1000
800
600
400
200
0
1055
261
1117
278
844
204
All cohort
Migraines With Aura
Migraines Without Aura
Before PFO closure
After PFO closure


Effect of residual right-to-left shunt
100%
80%
60%
40%
20%
0%
P= 0.032
91%
76%
P= 0.393
50%
41%
Migraine Burden Improvement
Migraine Abolishment
No residual right-to-left shunt
Residual right-to-left shunt


Effect of Aura
100%
80%
60%
40%
20%
0%
P= 0.576
88%
84%
P= 0.006
55%
24%
Migraine Burden Improvement
Migraine Abolishment
Migraines with Aura
Migraines without Aura


PFO
Cryptogenic
Stroke
Migraine

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

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Abstract

Objectives: To evaluate the long-term effect of transcatheter patent foramen ovale (PFO) closure on migraineurs with and without aura, and to 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: We 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 (minutes), and migraine burden (days*minutes/month). Improvement following closure was defined as complete abolishment of symptoms or > 50% reduction in migraine burden.

Results: 110 migraineurs who underwent PFO closure were included. 77% had aura and 23% without aura. 91% had a cryptogenic stroke. During long-term median follow-up of 3.2 (IQR 2.1- 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% of patients, and symptoms were completely abolished in 48%. Presence of aura was associated with abolishment of migraine (OR 4.3 [95% CI 1.5-12.3]; 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% (OR 4.6 [95% CI 1.3-16.1]; p=0.017).

Conclusions: Long-term follow up after transcatheter PFO closure was associated with significant improvement in migraine burdeiguren. Aura was a predictor of abolishing symptoms.

Absence of residual right-to-left shunt was a predictor of significant reduction in migraine burden.

Key Words: Patent Foramen Ovale; Migraine; Right to left shunt

Condensed Abstract: The association between PFO and migraine type headache is well established. Data regarding the benefit of transcatheter PFO closure in reducing migraine symptoms are conflicting. We have followed 110 migraineurs patients for 3.2 years after PFO closure and demonstrated a significant improvement in migraine symptoms. Notably, the presence of aura was a predictor of abolishing symptoms, and absence of residual right-to-left shunt was a predictor of significant reduction in migraine burden. This novel insight regarding the pathophysiology of PFO and migraines may assist in characterizing the migraineurs subpopulation that will likely benefit from PFO closure.

Abbreviation list: PFO=Patent Foramen Ovale; TTE = Trans-thoracic echocardiogram; TEE= Trans-esophageal echocardiogram.

Introduction

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 2-3 fold the expected prevalence of migraine compared to 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 and/or shunting of humoral vasoactive factors that escape degradation in the pulmonary circulation (3, 6, 7).

Multiple studies have reported improvement in migraine symptoms after transcatheter PFO closure (1, 5, 9–11), yet three randomized trials that followed patients for 6-12 month, failed to reach their primary endpoints (12–14). Interestingly in all of these randomized studies there were sub-groups 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 to 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 (MGH) 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 MGH 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 O2 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 (CT) imaging of the brain, carotid doppler ultrasonography, magnetic resonance imaging (MRI) of the brain, 12-lead electrocardiogram (ECG), 2-4 weeks of cardiac event monitoring, 2-D echocardiography (transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE) with bubble study with and without the Valsalva maneuver, standard blood test and hypercoagulable work-up (protein C and S, anti-thrombin III, lupus anticoagulant, anti-cardiolipin 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, Inc) or any of the Amplatzer PFO occluder, septal occluder or Cribiform devices (Abbott medical). The procedure was mostly performed under conscious sedation with few cases under general anesthesia. Patients were systemically anticoagulated with intravenous heparin (70-100 Units/kg). All patients underwent diagnostic right heart catheterization prior to device implantation. PFO closure device was deployed under both fluoroscopic and echocardiographic guidance with either intracardiac echocardiography (ICE) or TEE. 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 ECG were obtained 24 hours after the procedure and before hospital discharge. Following the procedure, patients were treated with daily aspirin 325 mg for six 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 (Supplemental material). 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: A) migraine frequency, defined as the number of days with headache per month. B) migraine duration, defined as the average duration of headache episodes in minutes. C) migraine burden, calculated as migraine frequency multiplied by the average duration of each episode (12). Migraine improvement following closure was defined as: A) complete abolishment of symptoms; B) >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 five 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 trans-thoracic echocardiogram at 6 months post PFO closure. Mild shunt was defined as 1-10 bubbles appearing in the left atrium, moderate shunt as 11-30 bubbles and large shunt as >30 bubbles appearing in the left atrium.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation and compared using Student's t-test, paired 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 percentages (%) and compared using Chi-square or Fisher’s 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, presence of atrial septum aneurysm and 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 non-significant. All p values were 2-sided, and values <0.05 were considered statistically significant. All data were analyzed using SPSS, Version 20.0 (IBM Corp., Armonk, NY).

Results

We identified 110 patients with migraine type headaches who underwent transcatheter PFO closure and who completed ≥12 months follow-up. Eighty-five (77%) patients had aura and 25 (23%) had migraine without aura. Atrial septal aneurysm was found in 30 (28%) patients. Right to left shunt was noticed at rest in 69 (64%) patients. Degree of the shunt was mild in 75%, moderate in 21% and large in 4%. Indications for PFO closure in our migraineurs cohort included 100 patients (91%) with PFO-related neurological embolic events (stroke: n=84, TIA: n=16), and 10 patients (9%) with platypnea-orthodeoxia or exercise-induced hypoxia. Baseline demographics and PFO related echocardiographic characteristics are summarized in **Table 1**. Apart from older age in 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 patient without indication for long term anticoagulation were treated with daily aspirin 325 mg for 3-6 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 migraineurs (19%) 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 day/month*minutes; p= 0.42).

Peri procedural complications included 1 patient (0.9%) with pericardial effusion, 2 patients (1.8%) with atrial fibrillation and 1 patient (0.9%) with device embolization. There was no periprocedural death. During the study follow up 2 patients (1.8%) had recurrent stroke and 1

patient (0.9%) had recurrent TIA. Four patients (3.6%) underwent repeat procedure due to persistence of significant interatrial shunt.

During median follow-up of 3.2 (IQR 2.1- 4.9) years after PFO closure, there was a significant decrease in all symptom criteria for the overall migraineurs population. In our cohort, 96 patients (87%) had reduced their migraine burden by >50% and 53 patients (48%) had abolished their migraine symptoms (**Table 2**). Four patients (3.6%) 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 to 2.1±4.3 days/month (p=0.006), Episode duration reduced from 322±355 to 294±359 minutes (p=0.001), and migraine burden reduced from 1409±1927 to 504±763 day/month*minutes (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%; p=0.57). However, migraine abolition occurred more frequently in migraineurs with aura (55% vs. 24%; unadjusted OR 3.9 [95% CI 1.4-10.7]; 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 4.3 [95% CI 1.5-12.3]; p=0.006) (**Table 3**).

At 6 months after PFO closure, residual right-to-left shunt of any severity was found in 29 (26%) patients (mild right to left shunt was detected in 18%, moderate in 7% and large in 1%). “Effective” closure, a term defined in stroke preventing studies (24) and includes procedures resulting with none or mild residual interatrial shunt, was reached in 92%. Rates of

residual right to left shunt were similar between migraineurs with or without aura (26% vs. 28%, respectively, p=0.83). As expected, the rate of acute post procedural right-to-left shunt imaged in the first 24 hours post procedure was higher than the residual right-to-left shunt noticed at 6 months (52% vs. 26 %). The majority (65%) of the acute post procedure residual shunts were trace/mild shunt.

Absence of right-to-left shunt at 6 months was more common in patients who had >50% reduction in migraine burden (77% vs 23%, unadjusted OR 3.36 [95% CI 1.1-10.6]; p=0.032) (**Table 3, Supplemental table**). Absence of residual right-to-left 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 4.6 [95% CI 1.3-16.1]; 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, 17, 18). There are PFO patients without migraines and there are migraineurs without PFO. Nevertheless, the symptomatic improvement in migraineurs post PFO closure seen in non-randomized 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 (IQR 2.1-4.9) years after PFO closure, we demonstrate that: (i) ≈90% of patients improved their migraine burden by >50% irrespective of the presence of aura, and ≈50% completely abolished their migraine symptoms, (ii) presence of aura was a significant predictor of complete abolishment of migraine symptoms following PFO closure, and (iii) 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 study (12) was a sham-controlled trial whos 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 (13) study 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 9-12 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). Lastly the PRIMIUM study (14) that was sham controlled, 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 non-significant 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 a highly symptomatic and refractory migraineurs patients, all had difficulties in recruitment and all 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.

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. Lastly, and most importantly, 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 to 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, 19). One such vasoactive substance is that has been implicated in migraine attacks is serotonin, and its metabolism involves degradation through lung monoamine oxidase (20). Interestingly, it has been found that plasma levels of serotonin decrease after percutaneous closure of PFO (21). Another mechanism that may contribute to the pathogenesis of right-to-left shunting and migraines, specifically in migraineurs with aura, is paradoxical micro-embolism (7, 17). 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). Anti-platelet drugs might prevent microemboli development as well as reduce the release of serotonin that can contribute to platelets aggregation. The finding that aspirin has a significant prophylactic effect on migraine (22), and clopidogrel reduces migraine attack frequency after transcatheter closure of PFO (23) 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-1 (19).

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 to 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 (24) might be sufficient to reduce the risk of cryptogenic stroke, mild residual shunts may still allow vasoactive metabolites as well as micro-emboli 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 in order 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 to follow up patients for longer periods. Regarding efficacy of device closure, we recommend evaluating residual right to left shunt at 6-12 months post closure and to consider including residual shunt analysis in the outcome metrics, as well as evaluating the role of "complete" vs. "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 mechanism that are not related to right-to-left shunting.

Our study has certain 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 patient with migraines. Nevertheless, as we described above, we believe that there is a unique relationship between 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, and specifically recall bias as 19% of our cohort did not complete the migraine burden questionnaire pre procedurally, and 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 has not been studied well in the literature and while some studies show complete endothelization at 12 weeks post procedure, other demonstrated that specific devices may have incomplete endothelialization even years after deployment. Lastly, 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. This did however, make our cohort homogenous allowing us to specifically examine the effect of residual shunt.

In conclusion, 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 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.

Perspective:

What is Known?

- The correlation between patent foramen ovale (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 following 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 migraineurs subpopulations that may benefit from PFO closure

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Figure Titles and Legends:

Figure 1 - Change in migraine frequency and burden after transcatheter PFO closure

Improvement in migraine frequency (upper panel) and migraine burden (lower panel) at 3.2 years after PFO closure. Migraine burden and frequency decreased significantly in both migraineurs with and without aura (Error bars represents standard error).

Central Illustration – Characterization of patients with migraine improvement after transcatheter PFO closure

At 3.2 years after PFO closure, 87% of our cohort reduced their migraine burden by >50% and 48% 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 panel) and migraine abolition occurred more frequently in migraineurs with aura (lower panel).

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 overlap separately or commonly with the other entities. The circles are scaled to approximately represent the overlap of the various entities based on published literature.

Table 1 – Baseline characteristics

	All cohort (n=110)	Migraine with Aura (n=85)	Migraine without Aura (n=25)	P value (+/- Aura)
Age	42.7 ± 11.5	41.5 ± 11.5	46.8 ± 10.5	**0.042**
Gender (female)	74 (67.3)	59 (69.4)	15 (60)	0.378
Hypertension	16 (14.5)	12 (14.3)	4(16)	0.832
Diabetes	4 (3.7)	4 (4.8)	0 (0)	0.266
Caucasian	104 (94.5)	80 (94.1)	24 (96)	0.716
Hypercoagulability	23 (21.3)	19 (22.9)	4 (16)	0.461
History of smoking	41 (37.3)	33 (38.8)	8 (32)	0.535
Arrhythmias	8 (7.3)	7 (8.2)	1 (4)	0.473
Family History of migraines	44 (40)	35 (41.2)	9 (36)	0.636
Atrial septal aneurysm	30 (27.8)	23 (27.7)	7 (28)	0.977
Interatrial shunt at rest	69 (63.9)	53 (63.9)	16 (64)	0.989
Presenting symptoms				
CVA/TIA	100 (90.9)	77 (90.5)	23 (92)	0.736
Hypoxia	10 (9.1)	5 (9.4)	2(8)	
Device Type				
Amplatzer PFO occluder	38 (34.5)	30 (35.3)	8 (32)	0.813
Amplatzer Septal occluder	21 (19.1)	16 (18.8)	5 (20)	
Amplatzer Cribriform	12 (10.9)	8 (9.4)	4 (16)	
CardioSEAL	39 (35.5)	31 (36.5)	8 (32)	

Data presented as mean +/- standard deviation, or n (%)

Table 2 – Improvement in migraine symptom metrics after PFO closure

		All cohort (n=110)		Migraines With Aura (n=85)		Migraines Without Aura (n=25)		P value (+/- Aura)
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	**P<0.001**	-2.9 ± 6.8	**P<0.001**	-1.9 ± 2.6	**P=0.001**	0.456
Average migraine duration (Minutes)	**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	**P<0.001**	-164 ± 155	**P<0.001**	-76 ± 111	**P=0.002**	**0.009**
Migraine burden (day/month * Minutes)	**Before PFO closure**	1055 ± 1508		1117 ± 1641		844 ± 922		0.428
	After PFO closure	261 ± 602		278 ± 670		204 ± 270		0.591
	Absolute Change	-794 ± 1410	**P<0.001**	-839 ± 1530	**P<0.001**	-640 ± 899	**P=0.002**	0.419
Reduced migraine burden >50%		96 (87.3%)		75 (88.2%)		21 (84%)		0.576
Migraine abolished		53 (48.2%)		47 (55.3%)		6 (24%)		**0.006**

Data presented as mean +/- standard deviation

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**
Greater than 50% Improvement in migraine burden						
Absence of Residual Shunt*	3.36	1.06 – 10.6	**0.039**	4.61	1.32 - 16.1	**0.017**
Aura	1.43	0.40 - 5.02	0.58	1.31	0.35 - 4.9	0.66
Gender	0.52	0.13 - 1.99	0.34	0.49	0.12 - 1.9	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 – 42.8	0.11	8.34	0.96 – 72.4	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 month post PFO closure