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Research article

Association of in situ thrombus within the patent foramen ovale and patients with migraine: A prospective cohort study

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ABSTRACT

Background: Patent foramen ovale (PFO) is associated with migraine; however, the mechanism of PFO-associated migraine is not well known; additionally, percutaneous closure is controversial. This study aimed to investigate in situ thrombi within the PFO and explore the possible predictors of the effectiveness of PFO closure in migraineurs.

Methods: This prospective cohort study included 48 asymptomatic patients and 92 migraineurs with PFO. Optical coherence tomography (OCT) was used to evaluate the PFO microstructure. Only migraineurs underwent percutaneous closure. Migraineurs were divided into two cohorts based on the presence of a thrombus within the PFO. The symptoms were assessed at the 12-month follow-up visit. Predictors were evaluated employing multivariate logistic regression and receiver operating characteristic curve analyses.

Results: In situ thrombi within PFO were identified in 69 migraineurs and in two asymptomatic patients (76.7 % vs. 4.3 %; $P < 0.001$). Additionally, endocardial irregularity, discontinuity, low signal, and spasm were found in 59 (65.6 %), 15 (16.7 %), 13 (14.4 %), and six (6.7 %) patients, respectively, in the migraine group. In situ thrombus was associated with migraine risk (OR 49.03; 95%CI 8.52–282.18; $P < 0.001$). At the 12-month follow-up of the migraineur cohort, the primary endpoint, a 50 % reduction in migraine frequency after closure (with or without thrombus in PFO) was met (85.3 % vs. 25.0 %; $P < 0.001$). In situ thrombus was associated with migraine relief (OR 6.75; 95%CI 1.28–35.56; $P = 0.024$).

Conclusions: In situ thrombus and abnormal endocardium within PFOs were common in migraineurs, and in situ thrombus was a risk factor for migraine. Percutaneous closure was more effective in migraineurs with thrombi within the PFO. OCT imaging improved the understanding of pathogenic PFOs and may be helpful in selecting suitable migraineurs for PFO closure.

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Abbreviations

PFO	Patent foramen ovale
OCT	Optical coherence tomography
RLS	Right-to-left shunt
TTE	Transthoracic echocardiogram
cTTE	Contrast transthoracic echocardiography
TEE	Transesophageal echocardiography
MIDAS	Migraine Disability Assessment Questionnaire
ESS	Endocardial shear stress
IQR	Interquartile range
OR	Odds ratio
CI	Confidence interval
AUC	Area under the curve
ROC	Receiver-operating characteristic

1. Introduction

Patent foramen ovale (PFO) has an estimated prevalence of 25 % in the adult population [1]. A right-to-left shunt (RLS) within PFO may be responsible for a variety of pathological processes, notably migraine and cryptogenic stroke. Multiple studies have suggested an association between PFO and migraine [2]. Nevertheless, the symptomatic improvement in migraineurs after PFO closure observed during nonrandomized studies was not reproducible in the three largest randomized clinical trials [3–5]. To date, the evidence has been controversial because of the lack of adequately dimensioned prospective and pathogenesis studies.

Migraine is a common neurological disease affecting almost 13 % of the general population and ranks among the top five causes of years lived with disability [6]. Unfortunately, current medications are either poorly tolerated by or ineffective in many migraineurs [7]. The mechanisms underlying PFO-associated migraine are not well understood. The most plausible pathophysiological theory connecting PFO and migraine is cortical spreading depression, which, in this case, is triggered by paradoxical cerebral thromboembolism, metabolite shunting, and transient hypoxemia [2]. Paradoxical embolism is defined as the migration of a thrombus from the systemic venous to the arterial circulation via an RLS. However, explaining why numerous PFO patients who encounter paradoxical embolism, a relatively infrequent event, do not experience pulmonary embolism remains challenging. They often lack the risk factors for thrombosis and do not exhibit deep venous thrombosis, a source of paradoxical embolism. Hence, thrombus formation within the PFO has been suspected [8,9]. However, direct evidence supporting this theory is lacking. Recently, Yan et al. [10,11] demonstrated the presence of an in situ thrombus within the PFO in patients with cryptogenic stroke or migraine. Compared to that in the control group comprising migraineurs, patients with thrombi in the PFO had a higher risk of stroke. Nonetheless, no studies have explored the role of thrombi in migraine and PFO closure.

Furthermore, we hypothesized that in situ thrombus formation is a risk factor for PFO-induced migraines and a predictive factor for the effectiveness of PFO closure. Optical coherence tomography (OCT) is a light-based imaging modality that generates high-resolution cross-sectional images of the tissue microstructure and can detect thrombus and endothelial injury with high sensitivity and accuracy [12]. To demonstrate our hypothesis, we evaluated the in situ thrombus and endocardium within the PFO using OCT and completed a follow-up during this study.

2. Methods

2.1. Study design and participants

This study was a prospective cohort study. From November 2022 to January 2023, migraineurs or asymptomatic patients diagnosed with PFO admitted to Zhongshan Hospital, Fudan University were sequentially screened. Patients screened for PFO were diagnosed using contrast-enhanced transthoracic echocardiography (cTTE). Complete clinical examination, cerebral computed tomography or magnetic resonance imaging, electrocardiography, and echocardiography were performed for all migraineurs. Patients with other types of cardiovascular defects, congestive heart failure, or atrial fibrillation were excluded. All the patients were thoroughly evaluated by cardiologists, neurologists, and imaging specialists. In the migraine group, a diagnosis was established according to the third edition of the International Classification of Headache Disorders [13] with no evidence of stroke. Subjects had $\geq$2 migraine attacks per month and at least one year of migraine course, failed at least 2 different migraine preventive medications. Participants who met the inclusion criteria maintained a diary for more than 60 days. Migraine-preventive medications and their dosages did not change until the 12-month follow-up visit. In the asymptomatic group, PFO was an incidental finding on cTTE during routine examinations in subjects with high-risk activities, clinical conditions, or high-risk anatomical features related to PFO. The transesophageal echocardiography (TEE) examination were finished in all patients for confirming the PFO structure. Echocardiographic examinations were performed to meet the inclusion and exclusion criteria, echocardiography examinations, see **Supplemental Methods**. This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (B2022-452, 2022.9.2), and

written informed consent was obtained from all participants. Data supporting the findings of this study are available from the corresponding author upon request.

3. Optical coherence tomography

PFO-OCT was performed using a non-occlusive technique. The image acquisition method removes blood from the PFO channel using a transparent media flush without balloon obstruction and uses helical pullback imaging. Specifically, a guiding wire was passed through the PFO channel via the femoral venous access. The distal end of the guide wire is placed in the left superior pulmonary vein to establish the track. With a guiding catheter pointing toward the PFO along the guiding wire, PFO angiography was performed with a high-pressure syringe (flow rate: 6–7 ml/s, pressure: 300–400 PSI, volume: 30–40 ml) to flush the blood out of the PFO channel and reduce the scattering of red light by red blood cells, which made the OCT imaging clear. An OPTIS OCT system (Abbott Vascular, Santa Clara, CA, USA) was used to evaluate the microstructure of PFO (Fig. S1). Images were automatically acquired at a pullback rate of 36 mm/s (180 fps). All images were digitally stored and analyzed using OPTIS software (Abbott Vascular).

The thrombus and endocardium within the PFO were evaluated based on the evaluation principles of OCT in the coronary artery [12]. The thrombus by OCT appears as an irregular mass attached to endocardial surface or floating within the PFO. A free-floating thrombus is defined as an in situ thrombus with circumferential blood flow in the most distal aspect. The number and volume of in situ thrombi (irregular mass $\geq$100 μm) were calculated. The normal endocardium is smooth, continuous, and homogeneous. An abnormal endocardium is classified as having an irregularity, discontinuity, low signal, or spasm. An irregular endocardium is defined as a rough but continuous endocardium. Discontinuity is defined as an endocardial rupture. A low signal indicates a signal-poor region within the endocardium. Endocardial spasm refers to shrinkage of multiple consecutive positions in the endocardium that disappear after adjusting the position of the guiding catheter tip. All analyses of imaging data were performed at an independent core laboratory (Abbott Vascular Laboratory, Shanghai, China) after the transcatheter procedure by investigators who were blinded to the patient information.

3.1. PFO closure and follow-up

After OCT examination, percutaneous closure was performed using an Amplatzer PFO occluder (Abbott Laboratories) with fluoroscopic and echocardiographic guidance. Only migraineurs underwent percutaneous closure. Heparin (100 U/kg) was administered intravenously to maintain intraoperative anticoagulation therapy. Routine transthoracic echocardiogram (TTE) and 12-lead electrocardiography were performed 24 h after the procedure. Patients received daily aspirin 200 mg for 1 month, followed by daily aspirin 100 mg for 5 months.

In the migraine cohort, the subjects were divided into two groups according to the presence of a thrombus within the PFO. Participants returned at 1, 3, 6, and 12 months to review their headache diaries. The primary endpoint was the improvement of migraine frequency after percutaneous closure, defined as $\geq$ 50 % reduction in the monthly number of migraine attacks during months 10–12 after closure compared with the 60-day baseline phase before closure. The pre-specified secondary endpoints included the change of migraine frequency, the change of migraine duration, complete abolishment of symptoms and disability due to migraine according to the Migraine Disability Assessment Questionnaire (MIDAS). Follow-up data for all patients were obtained during clinic visits or via telephone interviews.

3.2. Statistical analysis

Continuous data were expressed as mean ± standard deviation or median (interquartile range [IQR]), and compared using Student's t-test or the Mann-Whitney *U* test. Quantitative data are described as frequencies and/or percentages, and compared using the chi-square or continuous correction for the chi-square test.

Multiple univariate logistic regression analyses were performed to investigate potential prognostic factors. To explore the association between clinical factors, migraine, and the effectiveness of closure, a multivariable logistic regression model was used. The variables included in the model were selected based on their clinical relevance and statistical significance as determined by univariate analysis. The results were expressed as odds ratios (OR) and a 95 % confidence intervals (CI). The discriminative performance of the model was assessed using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. A 2-sided P value < 0.05 was considered statistically significant. All analyses were performed using SPSS software (version 22.0; IBM Corporation, Armonk, NY, USA).

4. Results

4.1. Baseline characteristics

All 495 migraineurs with PFO and 102 asymptomatic patients with PFO were initially screened. Some patients in both groups had shunts other than the PFO, mainly due to the pulmonary arteriovenous shunt confirmed by cTEE. Thirty eight patients in the migraine group had other shunts, including 36 (7.3 %) with pulmonary arteriovenous shunts and two (0.4 %) with small atrial septal defect. There were 5 patients (4.9 %) with pulmonary arteriovenous shunts in the asymptomatic group. Finally, 92 patients in the migraine group and 48 patients in the asymptomatic group who consented to undergo OCT were enrolled. Of the 140 subjects, four subjects did

not complete the OCT because their PFO channels were not passed. Two participants dropped out of the study before the 12-month follow-up period (Fig. 1). Among this entire cohort, the mean age between the migraine group and the asymptomatic group was 32.5 ± 7.9 and 34.9 ± 8.4 years, respectively. More than half of the patients in the migraine group were women (60.9 % vs. 58.3 %), and forty-four (47.8 %) patients had migraine with aura. Compared to the migraineurs without thrombus group, the migraineurs with thrombus group showed more patients with aura (55.1 % vs. 19.0 %, P = 0.004. Table 1).

In both the entire cohort and the migraine cohort, PFO lengths and heights were similar between the groups. An atrial septal aneurysm was detected in ten (10.9 %) migraineurs, but none of the asymptomatic patients had an atrial septal aneurysm (P = 0.043). Moreover, all ten migraineurs with atrial septal aneurysms had thrombi within the PFOs (Table 1). The functional characteristics of the PFO were evaluated based on RLS grade following cTTE results. Compared with those of the asymptomatic patients, migraineurs had a lower RLS grade at rest (P = 0.017) and a greater RLS change from the quiescent condition to the Valsalva maneuver (P = 0.001). The RLS grade after the Valsalva maneuver, which is the highest RLS grade, was not significantly different between the migraine and asymptomatic groups (P = 0.153). A provoked RLS (grade 0 at rest) was noted in 47 migraineurs and 17 asymptomatic patients (51.1 % vs. 35.4 %; P = 0.077). In the migraine cohort, there were no significant differences in the RLS grade at rest or Valsalva maneuver, RLS change, or provoked RLS between migraineurs with and without thrombus (Fig. S2).

4.2. Microstructure of PFO and risk factors for migraine

A total of 90 migraineurs and 46 asymptomatic patients successfully completed the OCT examination. Within the PFO channel, in situ thrombi were identified in 69 migraineurs and two asymptomatic patients (76.7 % vs. 4.3 %; P < 0.001). The migraine and asymptomatic groups differed significantly in terms of thrombus number per patient, total thrombus volume, and maximum thrombus area (all P < 0.001). All thrombi identified using OCT appeared as white thrombi that are less backscattered, homogeneous and had low attenuation. Additionally, 66 patients in the migraine group (73.3 %) and seven in the asymptomatic group (15.2 %) exhibited abnormal endocardium within the PFOs (P < 0.001). The endocardium of migraineurs showed more endocardial irregularity (65.6 % vs. 10.9 %; P < 0.001) and discontinuity (16.7 % vs. 0.0 %; P = 0.003). Irregular endocardial surfaces with thrombi attached were detected in 62 migraineurs and two asymptomatic patients (68.9 % vs. 4.3 %; P < 0.001). Examples of in situ thrombi and abnormal endocardium within the PFO are shown in Fig. 2A–F. Comparisons of in situ thrombi and abnormal endothelium within the PFO between groups are shown in Table 2.

In the univariate logistic regression analysis, several factors were significantly associated with migraineurs with PFO. These factors included in situ thrombus within the PFO, thrombus number per patient, maximum thrombus area, endocardial irregularity, and a high RLS gradient (all P < 0.01). However, atrial septal aneurysm and maximum RLS grade were not significantly associated with migraine (Table S1). Multivariable regression model revealed that in situ thrombus (OR 49.03; 95%CI 8.52–282.18; P < 0.001) and high RLS gradient (RLS change grade = 3: OR 8.30; 95%CI 1.10–62.80; P = 0.040) were associated with migraine in PFO patients. Table S2 shows the effect estimates of these covariates after adjusting for age, sex, body mass index and antithrombotic therapy.

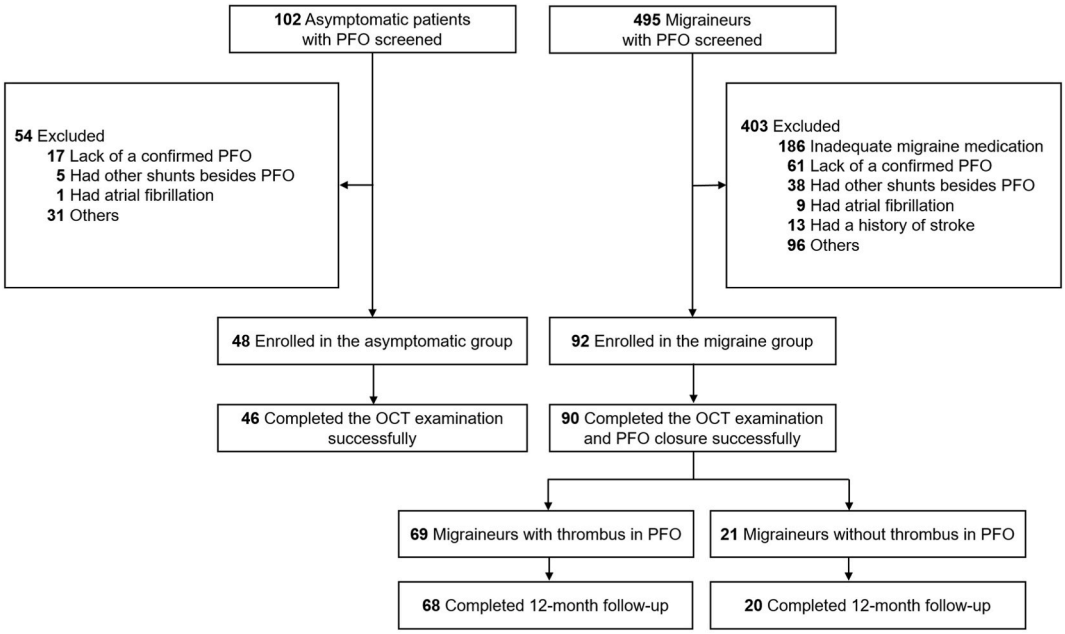

Fig. 1. Study Flowchart. Reasons for exclusion, considered "others", comprised intolerance to TEE, allergy to contrast agents, presence of other types of headache, history of coronary artery disease or other structural heart disease. Abbreviations: PFO, patent foramen ovale; OCT, optical coherence tomography.

Table 1
Clinical and PFO characteristics of the patients.

Variable	Entire cohort			Migraineur cohort		
	Asymptomatic patients (n = 48)	Migraineurs (n = 92)	P value	Without Thrombus (n = 21)	With Thrombus (n = 69)	P value
Clinical Characteristics						
Age, y	34.9 ± 8.4	32.5 ± 7.9	0.097	33.2 ± 7.5	32.2 ± 8.2	0.601
Males	20 (41.7)	36 (39.1)	0.771	11 (52.4)	24 (34.8)	0.147
BMI*, kg/m^2	23.0 ± 2.3	22.4 ± 2.4	0.167	23.1 ± 2.2	22.2 ± 2.4	0.166
Hypertension	7 (14.6)	9 (9.8)	0.397	1 (4.8)	8 (11.6)	0.618
Diabetes	4 (8.3)	4 (4.3)	0.561	1 (4.8)	3 (4.3)	1.000
Hyperlipidemia	3 (6.3)	7 (7.6)	1.000	2 (9.5)	5 (7.2)	1.000
Smoking	6 (12.5)	18 (19.6)	0.292	3 (14.3)	15 (21.7)	0.663
Antiplatelet agents	3 (6.3)	8 (8.7)	0.857	2 (9.5)	6 (8.7)	1.000
Aura	/	44 (47.8)	/	4 (19.0)	38 (55.1)	0.004
Echocardiography findings						
LAD, mm	32.1 ± 5.1	33.3 ± 4.8	0.165	33.2 ± 4.0	33.4 ± 5.1	0.820
PASP, mmHg	27.9 ± 3.9	28.9 ± 3.7	0.156	27.7 ± 3.9	29.2 ± 3.6	0.128
LVEF, %	65.0 ± 2.7	66.0 ± 3.3	0.116	64.7 ± 2.8	66.4 ± 3.3	0.062
PFO length†, mm	8.7 ± 3.3	9.8 ± 4.1	0.100	9.3 ± 4.3	10.0 ± 4.1	0.502
PFO height†, mm	1.8 ± 0.7	1.6 ± 0.7	0.182	1.5 ± 0.6	1.7 ± 0.7	0.410
Atrial septal aneurysm	0 (0)	10 (10.9)	0.043	0 (0)	10 (14.5)	0.146

Values are mean ± SD or n (%).Abbreviations: BMI, Body mass index; PFO, patent foramen ovale; LAD, left atrial diameter; PASP, pulmonary artery systolic pressure; LVEF, left ventricular eject fraction. * Calculated as weight in kilograms divided by height in meters squared. † The length and height of PFOs were measured using transesophageal echocardiography. P values are from Student's t-test, chi-square test or continuous correction for chi-square test.

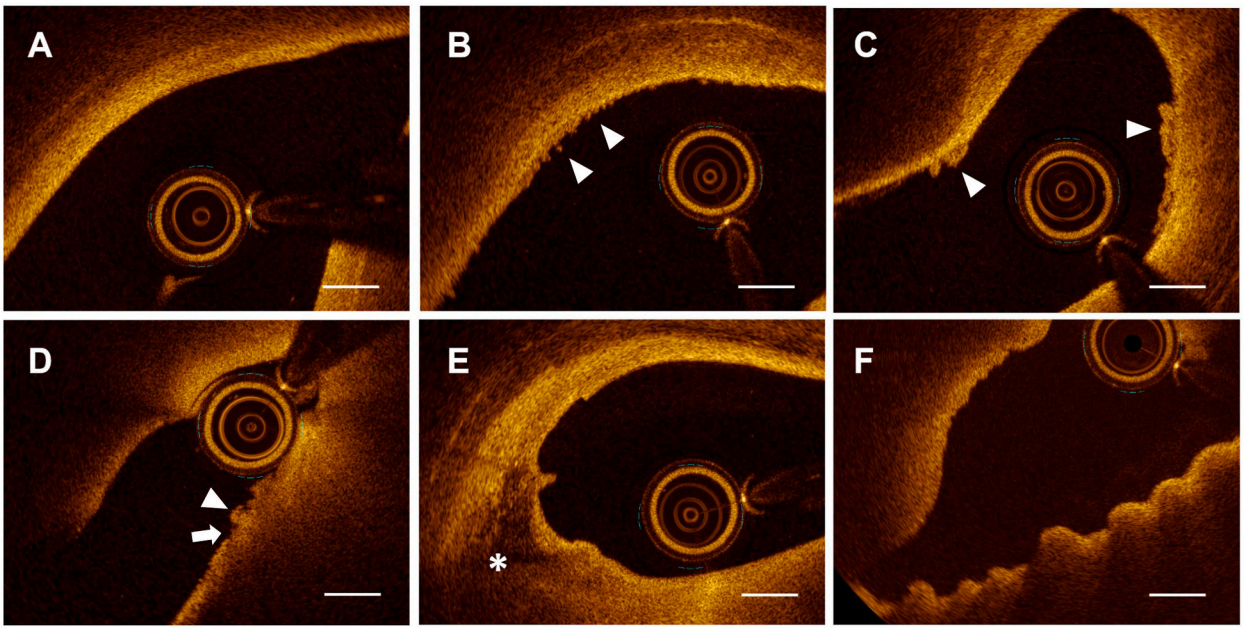

Fig. 2. In situ Thrombus and Abnormal Endocardium Within Patent Foramen Ovale. (A) Smooth endocardium without a thrombus (normal). (B) Irregular endocardial surface with free-floating thrombi (arrowhead). (C) Irregular endocardial surface with attached mural thrombi (arrowhead). (D) Discontinuous endocardial surface (arrow) with a thrombus (arrowhead). (E) Low signal (asterisk) in endocardium. (F) Endocardial spasm. Scale bars represent 500 μm.

4.3. Improvement in migraine after PFO closure

To determine which migraineurs would benefit from PFO closure, a 12-month follow-up was conducted, dividing the migraineurs into two groups based on the presence or absence of thrombus within PFO. In the migraine cohort, the primary endpoint, a 50 % reduction in migraine frequency (with or without thrombus in PFO), was met (85.3 % vs. 25.0 %; $P < 0.001$). Regarding the secondary endpoints, there was a significant decrease in migraine frequency, average migraine duration and MIDAS score. Migraine abolishment

Table 2
In situ thrombus and abnormal endothelium within the PFO.

Characteristics	Entire cohort (n = 136)	Asymptomatic group (n = 46)	Migraine group (n = 90)	P value
In situ thrombus within PFO				
Patients with in situ thrombus within PFO	71 (52.2)	2 (4.3)	69 (76.7)	<0.001
Patients with free-floating thrombus	26 (19.1)	0 (0.0)	26 (28.9)	<0.001
Thrombi per patient	2.0 (0.0–10.8)	0.0 (0.0–0.0)	5.5 (1.8–16.0)	<0.001
Total thrombus volume, mm^3	0.004 (0.000–0.041)	0.000 (0.000–0.000)	0.022 (0.003–0.055)	<0.001
Maximum thrombus area, mm^2	0.02 (0.00–0.05)	0.00 (0.00–0.00)	0.04 (0.02–0.07)	<0.001
Abnormal endocardium within PFO				
Irregular endocardial surface	64 (47.1)	5 (10.9)	59 (65.6)	<0.001
Discontinuous endocardial surface	15 (11.0)	0 (0.0)	15 (16.7)	0.003
Low signal	16 (11.8)	3 (6.5)	13 (14.4)	0.175
Spasm	6 (4.4)	0 (0.0)	6 (6.7)	0.177

Values are median (IQR) or n (%). Abbreviations: PFO, patent foramen ovale; IQR, interquartile range. P values are from Mann-Whitney *U* test, chi-square test or continuous correction for chi-square test.

occurred more frequently in migraineurs with thrombus in PFO (66.2 % vs. 10.0 %; P < 0.001). The baseline and follow-up data on migraine symptoms in migraineurs are shown in Table 3 and Fig. S3.

At the 12-month follow-up assessment of the migraine cohort, the univariate analysis revealed that in situ thrombus, thrombus number per patient, total thrombus volume, maximum thrombus area, and endocardial irregularity were associated with migraine improvement after PFO closure (Tables S3 and S4). The multivariable regression model indicated that in situ thrombus (OR 6.75; 95% CI 1.28–35.56; P = 0.024) and endocardial irregularity (OR 7.52; 95%CI 1.88–30.12; P = 0.004) were prognostic factors for a ≥50 % reduction in migraine frequency and also predictive factors for complete cessation of migraines. However, traditional predictors, including maximal RLS grade, atrial septal aneurysms, and aura, were not significantly associated with migraine improvement. Table 4 presents the multivariate analyses results of migraineurs after PFO closure adjusted for age, sex, body mass index, and antithrombotic therapy.

The ROC curve analysis indicated an AUC of 0.76 (95 % CI: 0.66–0.86; P < 0.001) for in situ thrombus and 0.86 (95 % CI: 0.76–0.95; P < 0.001) for the combined prediction model, which had better predictive value compared with that of other traditional parameters including aura, maximum RLS grade and atrial septal aneurysm (Fig. S4, Table S5). The presence of in situ thrombus showed a sensitivity of 92.1 %, a specificity of 60 %, a positive predictive value of 85.3 %, and a negative predictive value of 75.0 % for migraine relief.

4.4. Procedural complications

Following OCT examination, all 46 asymptomatic PFO patients concluded the procedure without undergoing PFO closure. All 90 migraineurs successfully underwent percutaneous PFO closure using an occluder. No immediate residual shunt was detected on postoperative TTE. No periprocedural complications, including pericardial effusion, device embolization, arrhythmia, stroke, or bleeding, occurred. One patient in the migraine group experienced a migraine attack during the OCT procedure, and in situ thrombi were identified within the PFO. No abnormal brain findings were observed on postoperative computed tomography.

Table 3
Improvement in migraine symptom after PFO closure.

	Migraine cohort (n = 88)		Migraineurs Without Thrombus in PFO (n = 20)		Migraineurs With Thrombus in PFO (n = 68)		P Value ± Thrombus
	Data	p Value	Data	p Value	Data	p Value	
Reduced migraine frequency ≥ 50 %	63 (71.6)		5 (25.0)		58 (85.3)		<0.001
Migraine frequency, n/month							
Before PFO closure	5.3 ± 2.0		5.2 ± 2.1		5.4 ± 1.9		0.749
After PFO closure	2.0 ± 2.5		4.7 ± 2.4		1.2 ± 2.0		<0.001
Absolute change	−3.4 ± 2.8	<0.001	−0.5 ± 2.3	0.340	−4.2 ± 2.4	<0.001	<0.001
Migraine duration, hours							
Before PFO closure	10.1 ± 7.0		10.7 ± 7.6		9.9 ± 6.9		0.699
After PFO closure	4.1 ± 5.7		8.7 ± 7.5		2.8 ± 4.3		0.003
Absolute change	−5.9 ± 6.2	<0.001	−2.0 ± 4.4	0.061	−7.1 ± 6.2	<0.001	<0.001
Migraine abolition	47 (53.4)		2 (10.0)		45 (66.2)		<0.001
MIDAS score							
Before PFO closure	39.1 ± 17.0		40.4 ± 20.3		38.7 ± 16.1		0.737
After PFO closure	16.0 ± 20.1		30.8 ± 20.2		11.7 ± 18.0		0.001
Absolute change	−23.1 ± 19.7	<0.001	−9.7 ± 15.2	0.011	−27.0 ± 19.3	<0.001	<0.001

Values are mean ± SD or n (%). Abbreviations: PFO, patent foramen ovale. MIDAS, Migraine Disability Assessment Questionnaire; P values are from Student's t-test, paired Student's t-test or chi-square test.

Table 4
Multivariate analysis of prognostic factors for the improvement in migraine symptom after PFO closure.

Variable Comparison		Reduced migraine frequency ≥50 %		Migraine abolition	
		OR (95 % CI)	P value	OR (95 % CI)	P value
In situ thrombus		6.75 (1.28–35.56)	0.024	10.05 (1.71–59.20)	0.011
Endocardial irregularity		7.52 (1.88–30.12)	0.004	4.48 (1.32–15.20)	0.016
Maximum RLS grade	Grade 1	Reference		Reference	
	Grade 2	0.40 (0.02–8.82)	0.562	1.15 (0.12–10.63)	0.905
	Grade 3	0.76 (0.03–16.95)	0.862	3.99 (0.47–33.63)	0.203
Atrial septal aneurysm		3.21 (0.20–51.28)	0.409	2.20 (0.36–13.50)	0.395
Aura		2.41 (0.50–11.53)	0.270	1.37 (0.45–4.24)	0.581

The association between improvement in migraine symptom after PFO closure and related factors were estimated in multivariable logistic model adjusted for age, sex, body mass index and antithrombotic therapy. Abbreviations: PFO, patent foramen ovale; RLS, right-to-left shunt; OR, odds ratio; 95 % CI, 95 % confidence interval.

5. Discussion

The role of PFO in migraine remains intrinsically elusive. To our knowledge, this is the first prospective cohort study on in situ thrombus and abnormal endocardium within the PFO of migraineurs. In this study, in situ thrombi and abnormal endocardial structures within PFOs were commonly detected in migraineurs, and in situ thrombi were found as a risk factor for migraine. During the follow-up period, percutaneous PFO closure was more effective in relieving migraines in migraineurs with thrombus and abnormal endocardium within the PFO. These findings suggest a new mechanism for PFO- associated migraines and predictors for screening suitable patients who will benefit from PFO closure.

OCT is an intraluminal imaging method with a high resolution of approximately 10 μm [12]. It can accurately detect the microstructure of tissue and is widely applied for evaluating plaque erosion and thrombus in coronary artery [14,15]. This study utilized OCT to thoroughly assess the endocardium of the PFO channel in vivo. We found that 76.7 % of migraineurs had in situ thrombus within the PFO channel. We speculated three reasons why not all migraineurs exhibited in situ thrombus within the PFOs in this study: 1) thrombi within the PFOs may have dislodged at the time of detection; 2) the association between the PFO and migraine is mediated by other mechanisms, some of which depend on shunting of humoral vasoactive factors; and 3) although rigorous screening was performed, some enrolled migraineurs may have symptoms attributable to causes other than PFOs. Microembolisms triggering focal transient cerebral ischemia and cortical spreading depression play major roles in migraineurs without neuroimaging abnormalities [16,17]. Yan et al. [10,11] reported that in situ thrombi were detected within the PFOs of patients with cryptogenic stroke or migraine. Migraine is considered a risk factor for future ischemic stroke [18,19]. These two PFO-attributable diseases may have similar pathogenic mechanisms. We also found that an in situ thrombus within the PFO was an independent risk factor for migraines.

Currently, the mechanism of in situ thrombus formation within the PFO channel remains unclear. Analogous to the coronary thrombosis mechanism, the abnormal endocardium, which was frequently detected in migraineurs in this study, likely plays a significant role. In situ thrombi were identified as white (platelet-rich) thrombi on OCT. A white thrombus formed on an irregular but continuous endocardial surface was the most common lesion within the PFOs of migraineurs. This lesion closely resembles plaque erosion [12]. Therefore, we proposed the concept of “endocardial erosion” for the first time. Although the underlying mechanism is unknown, endocardial erosion shares many similarities with plaque erosion. Unlike traditional vulnerable plaques and plaque ruptures, plaque erosion has unique clinical characteristics, such as younger age, female sex, and the absence of traditional cardiovascular risk factors [20,21], which are also significantly associated with PFO-attributable embolism [9]. Patients enrolled in our study also had these characteristics. In addition, endocardial spasms were observed within the PFO. Vasospasm has been suggested as a cause of endothelial damage and subsequent thrombosis [22]. We speculated that endocardial spasm was one of the reasons for the thrombi within the PFO. In coronary arteries, areas with low signal or poorly defined borders are termed as “lipid pool” [12,15], but their nature in endocardium remains unknown. These abnormal endocardium types may be associated with thrombosis within the PFO.

A shunt within a PFO can create endothelial or endocardial shear stress (ESS). Several OCT-based computational fluid dynamics studies have demonstrated a change in local hemodynamics and high ESS in plaque erosion [23–25]. However, a recent study revealed that high ESS gradient, rather than ESS, may play a more critical role [26]. In this study, we evaluated the RLS using cTTE. Interestingly, there was no difference in RLS within the PFOs during the Valsalva maneuver between migraineurs and asymptomatic patients. However, the RLS within the PFOs of migraineurs showed a greater change after the Valsalva maneuver, suggesting that migraineurs might have higher oscillatory shear stress within the PFO, which contributed to endocardium erosion and thrombus formation. This is solely a hypothesis, and further hydrodynamic research is necessary to confirm cause of endocardial injury within the PFO.

To date, the use of percutaneous closure as a therapy for migraineurs with PFO remains controversial. The three largest randomized clinical trials [3–5] failed to demonstrate a statistically significant difference in primary outcomes between percutaneous closure and medical therapy. However, many secondary endpoints were significant in favor of closure. Therefore, it is important to select patients who would benefit from a percutaneous closure. This follow-up study revealed that migraineurs with thrombi in PFO had a higher improvement rate of symptoms after percutaneous closure (85.3 % vs. 25.0 %; $P < 0.001$). After correcting for relevant factors, in-situ thrombus and endocardial irregularity were identified as independent prognostic factors of PFO closure for migraine improvement. However, the maximal RLS grade, atrial septal aneurysm, and aura were not significantly associated with migraine improvement after

PFO closure. This may be owing to the insufficiently large sample size. In addition, these traditional predictors with low effectiveness may have led to negative trial results for PFO closure in migraineurs. Migraine was also improved in 25.0 % of migraineurs without thrombi, and was ceased completely in 10.0 % of these patients. This could be partly attributed to postoperative antithrombotic therapy [27–30]. On one hand, these results support the hypothesis that thrombus within the PFO induces migraine. On the other hand, OCT can aid in identifying migraineurs with thrombi in the PFO who stand to benefit more from closure.

Many meta-analyses have confirmed that PFO closure is significantly associated with burden reduction in migraineurs [31–33]. However, the proportion of end-point events varies between studies. For example, the responder rate and cessation rates of migraines were 38 % and 9 %, respectively, in the PREMIUM trial [5], while in an observational study by Ben-Assa [34], they were 87 % and 48 %. Our findings, with responder and cessation rates of 71.6 % and 53.4 %, respectively, were consistent with Ben-Assa's study. There are several possible explanations for this difference. First, the absence of residual shunts was correlated with a significant reduction in migraine burden. In addition, there may be a dose-effect relationship between the residual shunt and migraine symptoms [34,35]. As this study focused on the PFO microstructure in the closure effect, the follow-up of the residual shunt was not comprehensive. Subsequently, we will conduct examinations of residual shunt in a larger number of participants. Second, younger patients benefit more from PFO closure [2,36]. The average age of the participants was >40 years in many studies, whereas it was 32.5 years in our study. This younger cohort may have resulted in a higher response rate. Third, patients with refractory migraines may have a relatively poor prognosis. In the PREMIUM study with a lower responder rate, the participants must have failed a trial of at least three medications to be considered as refractory [5]. Conversely, our inclusion criteria considered the failure of two medications. In short, the effectiveness of RLS closure and the characteristics of the participants may have led to the different response rates.

This study had several limitations. First, this was a single-center study with a small number of patients and lacked long-term follow-up. Second, the evaluation of in situ thrombi and endocardial structures within PFOs may have been incomplete because of the limited field of view on OCT. Third, the formation mechanism of in situ thrombus and abnormal endocardium within the PFO remains largely unclear. Fourth, further prospective, large-scale and randomized controlled trials are warranted to clearly define the implications of OCT in treatment strategies for PFO.

6. Conclusions

In situ thrombi and abnormal endocardium within the PFO channel are commonly detected in migraineurs, and in situ thrombi were a risk factor for migraine. The most common lesion was a white thrombus formed on an irregular endocardial surface, which we termed "endocardial erosion". Percutaneous PFO closure may be more effective in migraineurs with thrombi within the PFO. The high resolution of OCT provides a greater understanding of the intrinsic morphological features of pathogenic PFO and may have predictive significance for the prognosis of migraineurs after closure. These findings suggest a new mechanism for PFO- associated migraine and predictors for screening patients who will benefit from PFO closure. Further randomized controlled studies are needed to determine whether OCT examination of PFO has guiding value for migraine treatment strategies.

Data availability statement

The dataset supporting the findings of this study is available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of Zhongshan Hospital, Fudan University, with the approval number: B2022-452. All participants provided informed consent to participate in the study.

Consent for publication

Not applicable.

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CRediT authorship contribution statement

Shiqiang Hou: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Zhi Zhan:** Formal analysis, Data curation, Conceptualization. **Jianing Fan:** Formal analysis, Data curation, Conceptualization. **Mingfei Li:** Project administration, Formal analysis. **Shasha Chen:** Methodology, Data curation. **Yuan Zhang:** Project administration, Formal analysis. **Yuliang Long:** Methodology, Investigation. **Wenzhi Pan:** Supervision, Conceptualization. **Xiaochun Zhang:** Supervision, Project administration, Conceptualization. **Daxin Zhou:** Project administration, Investigation, Conceptualization. **Junbo Ge:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32105.

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