Long-term Echocardiographic Features After Percutaneous Closure of Patent Foramen Ovale

Maja Rojko,[1] Natasa Cernic Suligoj,[1,2] Bojana Zvan,[1,3] Metka Zorc,[1,3] Saibal Kar[1,4] and Marko Noc[1,3,5]

1. MC Medicor International Center for Cardiovascular Diseases, Izola, Slovenia; 2. Department of Cardiology, General Hospital, Izola, Slovenia; 3. Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; 4. Los Robles Regional Medical Center, Thousand Oaks, CA, US; 5. Center for Intensive Internal Medicine, University Medical Center, Ljubljana, Slovenia

Abstract

Background: There is a lack of studies systematically addressing long-term echocardiographic features after patent foramen ovale (PFO) closure. Thus, the present study investigated long-term echocardiographic features after percutaneous closure of PFO. **Methods:** This was a single-centre observational study based on the institutional registry of consecutive patients undergoing PFO closure. Clinical and echocardiographic features during the follow-up were investigated. **Results:** Between 2006 and 2023, 355 consecutive patients underwent PFO closure following transitory ischaemic attack (TIA) or cerebrovascular insult (CVI). Echocardiography immediately after the procedure and at 6 months was performed in 306 (86%) patients, who had repeat examinations at either between 1 and 5 years (median 1.32 years), between 5 and 10 years (median 7.10 years) or after 10 years (median 11.64 years). The percentage of patients with complete closure (no bubbles during the Valsalva manoeuvre) increased from 64% after the procedure to 80% at 6 months ($p<0.05$), and ranged between 77% and 81% thereafter (NS). Functional closure (≤10 bubbles) was observed in 93% of patients after the procedure and remained between 94% and 97% thereafter (NS). Except for decreased immediate complete closure (60% versus 83%; $p<0.001$), there was no difference between the Amplatzer PFO occluder and alternative devices. Among the 15 patients with greater than moderate residual shunt, reasons for the shunt were determined in 73% of patients and included leakage at the level of device, fenestration/atrial septal defect and pulmonary arteriovenous malformation. There was no late device embolisation, thrombus formation or pericardial effusion. Clinical follow-up revealed recurrent TIA and CVI rates of 0.11 and 0.06 per 100 patient-years, respectively. **Conclusion:** We demonstrated high (>90%) and persistent functional PFO closure beyond 10 years, independent of closure device. There was no late device embolisation, thrombus formation or pericardial effusion. Favourable echocardiographic features were associated with very low rates of recurrent TIA or CVI.

Keywords

Patent foramen ovale closure, residual shunt, echocardiography

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Data availability: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Authors' contributions: Conceptualisation: MR, MN; data curation: MR; formal analysis: MR; funding acquisition: MZ; investigation: MR, NCS; methodology: MN, SK, BZ; project administration: MR; resources: MZ; supervision: MN, MZ; validation: SK, BZ; visualisation: MR, MN; writing – original draft preparation: MR; writing – review & editing: MN

Ethics: This study was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Approval for the study was granted by the National Medical Ethics Committee of the Republic of Slovenia (No. 0120-46/2022/9).

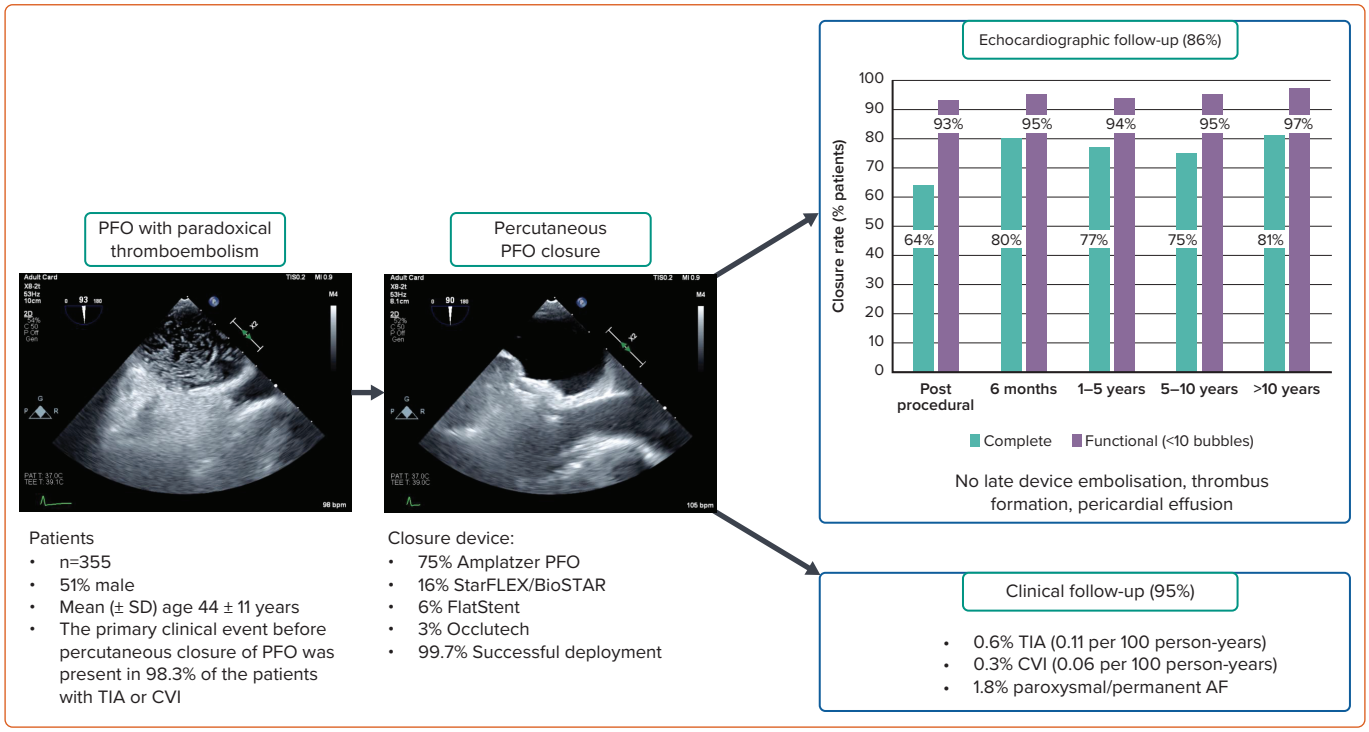
Consent: Written informed consent was obtained from all individuals included in the study.

Correspondence: Marko Noc, MC Medicor International Center for Cardiovascular Diseases, Polje 40, 6310 Izola, Slovenia. E: marko.noc@mf.uni-lj.si

Percutaneous closure of patent foramen ovale (PFO) is viewed as an evidence-based intervention for the secondary prevention of paradoxical thromboembolic events, including transitory ischaemic attack (TIA) and cerebrovascular insult (CVI).[1–3] Although a recent systematic analysis of observational and randomised trials demonstrated a low incidence of recurrent TIA/CVI, long-term echocardiographic features, including residual shunting and device morphology, are limited to a few observational studies with follow-up duration of <5 years.[4–6] Accordingly, potential very late complications, including the reappearance of right-to-left shunting, device embolisation, thrombus formation and erosion of adjacent cardiac structures resulting in perforation and pericardial effusion, are largely unknown.

Thus, in the present study, we sought to systematically evaluate long-term echocardiographic features and extended our follow-up to >10 years. At different time intervals after PFO closure, we investigated the incidence of

Central Illustration: Echocardiography After Patent Foramen Ovale Closure



CVI = cerebrovascular insult; PFO = patent foramen ovale; TIA = transient ischaemic attack.

residual shunting, morphological features related to the closure device and adjacent structures, as well as possible differences between the Amplatzer PFO occluder and alternative devices. Furthermore, we investigated potential causes of significant residual shunting using transoesophageal echocardiography (TOE) and pulmonary CT angiography (CTA).

Methods

This is a single-centre observational study performed at MC Medicor International Center for Cardiovascular Diseases (Izola, Slovenia). The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (No. 0120-46/2022/9). All procedures were performed in accordance with the Declaration of Helsinki. Patients provided written informed consent for device implantation and follow-up, including clinical examination and echocardiography.

Indications for percutaneous PFO closure were discussed by the institutional PFO team, comprising the referring physician, vascular neurologist, dedicated echocardiographer and interventional cardiologist, as described previously.[7,8] Briefly, patients were eligible for percutaneous closure if they were aged ≥18 years, had CVI documented on CT or MRI, or TIA and PFO documented by TOE. Patients were routinely screened for other possible causes of CVI/TIA, including large vessel disease, such as aortic/carotid atherosclerosis, hypercoagulable state and paroxysmal AF, with 24-hour Holter monitoring if such events were suspected. If mechanisms other than paradoxical embolisation or lacunar infarct due to intrinsic small vessel disease were identified, PFO closure was not attempted.

PFO closure was performed in the cath lab by dedicated interventional cardiologists (MN, SK) and echocardiographers (MR, NCS). Conscious sedation without endotracheal intubation was used and the procedure was guided by fluoroscopy and TOE. After femoral vein access was achieved, a 6Fr multipurpose catheter (Cordis; Johnson & Johnson) was advanced over a J-tipped 0.035-inch guidewire (Cook Medical) into the right atrium and through the PFO into the left upper pulmonary vein. If PFO crossing was not successful with the J-tipped wire, a 0.038-inch hydrophilic wire (Radiofocus Guidewire M; Terumo) was used. After crossing the PFO, a weight-adjusted bolus of unfractionated heparin was administered and the wire was exchanged for a long, Amplatz Super Stiff guidewire (Abbott Vascular). Balloon sizing was left to the discretion of the operators. Different closure devices, including StarFLEX/BioSTAR (NMT Medical), FlatStent EF (Coherex), Occlutech (Occlutech) and the Amplatzer PFO occluder (Abbott Vascular), were used. Device selection was left to the discretion of the interventional cardiologist and echocardiographer and was based on the morphology of the PFO and adjacent structures, as well as the availability of a particular closure device. None of the patients received a dedicated occluder for atrial septal defect closure. Devices were implanted according to the manufacturers' instructions. Appropriate device shape and positioning were documented by fluoroscopy and TOE. After the procedure, patients received a loading dose of 300 mg clopidogrel, followed by 75 mg/day clopidogrel for 6 months and lifelong acetylsalicylic acid at 100 mg/day. Endocarditis prophylaxis was recommended for 6 months after device implantation.

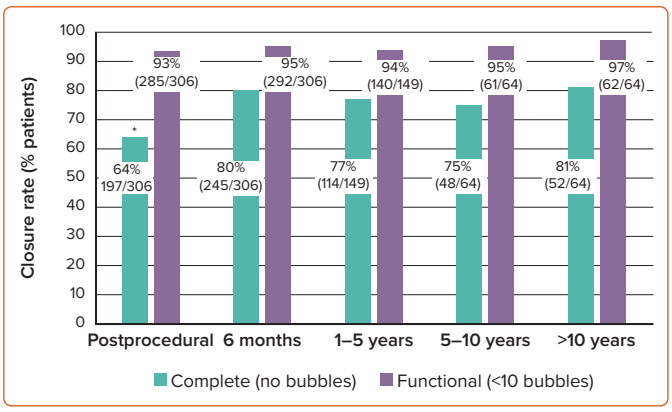
Immediate postprocedural PFO closure was investigated by TOE with the patient still on the cath lab table using a bubble study during the Valsalva manoeuvre or by applying and releasing hand pressure at the right upper abdomen. The bubble study was performed by injecting 10 ml of a mixture of saline (8 ml), patient blood (1 ml) and room air (1 ml) through the femoral sheath. The degree of right-to-left shunting was graded according to the appearance of bubbles in the left atrium within six cardiac cycles after right atrial opacification as large (>20 bubbles), moderate (10–20 bubbles) or small (<10 bubbles).[9,10] Functional PFO closure was defined as ≤10 bubbles.[10]

Table 1: Patient Characteristics and Procedural Features

Characteristics and Features	Patients (n=355)
Male sex	182 (51%)
Age (years), mean ± SD	44 ± 11
Indication for PFO closure	
TIA/CVI	349 (98.3%)
Thromboembolic acute MI	4 (1.1%)
Peripheral arterial thromboembolism	2 (0.6%)
Conscious sedation	333 (94%)
General anaesthesia/intubation/mechanical ventilation	22 (6%)
Echocardiographic guidance	
TOE	346 (97%)
ICE	9 (3%)
Sizing balloon	161 (45%)
PFO occluder	
Amplatzer	268 (75%)
BioSTAR	48 (14%)
FlatStent	21 (6%)
Occlutech	10 (3%)
StarFLEX	8 (2%)
Successful device deployment/stable position	354 (99.7%)
Device embolisation at implantation	1 (0.3%)
Residual shunt immediately after closure	
None	234 (66%)
Small (1–10 bubbles)	98 (28%)
Moderate (>10–20 bubbles)	22 (6%)

Unless indicated otherwise, data are given as n (%). CVI = cerebrovascular insult; ICE = intracardiac echocardiography; TIA = transient ischaemic attack; TOE = transoesophageal echocardiography.

Figure 1: Patent Foramen Ovale Closure Rate Assessed by a Bubble Study During the Valsalva Manoeuvre at Different Time Points After the Procedure



**p<0.05 compared with complete closure at the other time points.*

All patients underwent transthoracic echocardiography (TTE) with a bubble study at 6 months. The TTE bubble study was performed by injecting 10 ml of the saline–blood–air mixture described above into the right cubital vein. At the time of the rapid injection, the patient's arm was raised. The appropriateness of the Valsalva manoeuvre was confirmed by the shift of the interatrial septum from the right to the left atrium. The degree of right-to-left shunting was graded as described above using a four-chamber apical view. The study was repeated at least three times. In addition to residual shunting, device position, morphology, possible thrombus formation and the presence of pericardial effusion were evaluated. Additional echocardiography (TOE or TTE) with a bubble study beyond 6 months was performed at the discretion of the patient's cardiologist or neurologist and with the patient's agreement.

Patients with at least moderate residual shunt (>10 bubbles during the Valsalva manoeuvre) underwent further diagnostic investigations, starting with TOE to define device–interatrial septum morphology and interaction, as well as the site of eventual leakage. If TOE did not reveal the cause of right-to-left shunting, pulmonary CTA was performed to document possible pulmonary arteriovenous malformation.

Clinical events during follow-up were documented on the basis of patient interviews, examinations and review of outpatient and hospital records.

Continuous variables are presented as the mean±SD or as median with interquartile range (IQR) depending on their distribution. Categorical variables are presented as numbers with percentages. Continuous variables were compared using unpaired two-tailed t-tests, whereas categorical variables were compared using χ^2 or Fisher's exact test. The McNemar Chi-squared test for dependent samples was used to compare echocardiographic closure rates at different time periods. In all cases, two-tailed $p<0.05$ was considered significant.

Results

Between October 2006 and October 2023, 364 consecutive patients underwent percutaneous PFO closure (*Supplementary Figure 1*). After exclusion of patients with concomitant atrial septal defect (n=7) and decompression illness (n=2), 355 patients with paradoxical thromboembolism were enrolled in the study.

The mean age of the patients enrolled in this study was 44 years, and most (98%) presented with TIA or CVI (*Table 1*). PFO closure was performed under conscious sedation (94%) using predominantly TOE guidance (97%) in addition to fluoroscopy (100%). A sizing balloon was used in 45% of patients. Most patients (75%) received an Amplatzer PFO occluder. Except for one case of embolisation (0.3%), which required surgical removal of the closure device from the mitral subvalvular apparatus, device deployment was successful in all patients. Immediate complete PFO closure was achieved in 66% of patients and functional closure (≤0 bubbles) was achieved in 94% of patients.

Clinical follow-up was completed in 337 (95%) patients, with median follow-up duration of 1,457 days (*Table 2*). Recurrent TIA was documented in 2 (0.6%) patients (0.11 per 100 patient-years) and CVI was documented in 1 (0.3%) patient (0.06 per 100 patient-years). Other clinical events included amaurosis fugax in 1 (0.3%) patient and unexplained blindness in 1 (0.3%) patient, which occurred 193 and 4,685 days after closure, respectively. AF, either paroxysmal or permanent, cumulatively occurred in 1.8% of patients. Death during the follow-up period was documented for 8 (2%) patients.

Echocardiographic follow up at 6 months was completed in 306 (86%) patients, who had repeat examinations either between 1 and 5 years (median 1.32 years), between 5 and 10 years (median 7.10 years) or after 10 years (median 11.64 years) (*Supplementary Figure 2*). The percentage of patients with complete closure increased from 64% after the procedure to 80% at 6 months ($p<0.05$) and ranged between 77% and 81% thereafter

Table 2: Long-term Clinical Follow-up After Percutaneous Patent Foramen Ovale Closure

Clinical Follow-up	Patients (n=355)
Complete long-term follow-up	337 (95%)
Duration of follow-up (days)	
Mean ± SD	1,957 ± 1,690
Median (IQR)	1,457 (267–3,447)
Clinical events and timing	
TIA (at 14 and 1,163 days)	2 (0.6%)
CVI (at 2,232 days)	1 (0.3%)
Amaurosis fugax (at 193 days)	1 (0.3%)
Unexplained blindness (at 4,685 days)	1 (0.3%)
PAF (at 42, 86 and 2,920 days)	3 (0.9%)
Permanent AF/AU (at 1,269, 4,450 and 4,463 days)	3 (0.9%)
Death	8 (2%)
Unknown cause (at 386, 1,482, 1,741 and 1,806 days)	4 (50%)
Malignancy (at 4,055 and 5,438 days)	2 (25%)
Liver cirrhosis (at 2,956 days)	1 (12.5%)
Traffic accident (4,397 days)	1 (12.5%)

Unless indicated otherwise, data are given as n (%). AU = atrial undulation; CVI = cerebrovascular insult; PAF = paroxysmal AF; TIA = transitory ischaemic attack.

(NS; *Figure 1*). Functional closure (≤10 bubbles during the Valsalva manoeuvre) was seen in 93% of patients after the procedure, and remained between 94% and 97% thereafter (NS).

Complete closure immediately after the procedure was lower with the Amplatzer PFO occluder than with alternative devices (60% versus 83%, respectively; p<0.001; *Table 3*). At 6 months and thereafter, there were no significant differences in complete closure rates. Functional PFO closure was comparable between the Amplatzer and non-Amplatzer devices immediately after the procedure (92% versus 97%, respectively; p=0.267) and thereafter exceeded 94%. There was no late device embolisation, migration, thrombus formation or pericardial effusion.

Identifiable reasons for moderate or greater residual shunt in 15 (4.9%) patients were leakage at the level of the closure device (n=6), uncovered fenestration (n=3), uncovered small atrial septal defect (n=1) and pulmonary arteriovenous malformation (n=1; *Figure 2*). In four patients, no reason for residual shunting could be identified by TOE or CTA. None of the 15 patients with moderate or greater residual shunt had any recurrent thromboembolic event and none underwent any repeat intervention.

Discussion

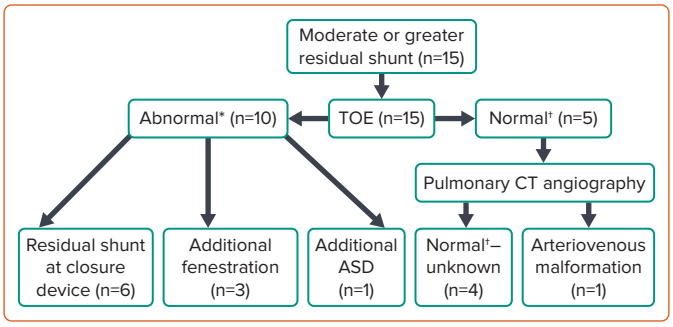
The main value of this study is the demonstration of a high rate of persistent functional PFO closure by echocardiography beyond 10 years after percutaneous closure. We thereby extend previous observations demonstrating >96% functional closure between 1 and 6 months and 91–94% at 4.5 years after the procedure.[5,6] Although the selection of closure devices was not randomised and, numerically, was not well balanced, we did not find any significant differences in functional closure rates between different devices. Interestingly, the Amplatzer PFO occluder was associated with less favourable complete closure immediately after the procedure, which may be best explained by the more rigid structure of this device, which requires more time to adapt to the PFO channel and interatrial septal anatomy.

Table 3: Complete and Functional Patent Foramen Ovale Closure According to Closure Device

Time Point	Closure	Amplatzer PFO Occluder, n (%)	Other Devices, n (%)	p-value
Immediately after procedure	Complete	144/242 (60%)	53/64 (83%)	<0.001
	Functional	223/242 (92%)	62/64 (97%)	0.267
At 6 months	Complete	193/242 (80%)	52/64 (81%)	0.790
	Functional	229/242 (95%)	63/64 (98%)	0.315
From 1 to >10 years	Complete	162/213 (76%)	52/64 (81%)	0.385
	Functional	201/213 (94%)	62/64 (97%)	0.533

Complete and functional PFO closure were defined as no bubbles and ≤10 bubbles on the Valsalva manoeuvre, respectively. PFO = patent foramen ovale.

Figure 2: Assessment of Mechanism Underlying Moderate or Greater Residual Shunt After Percutaneous Patent Foramen Ovale Closure



**Positive bubble study. †Negative bubble study. ASD = atrial septal defect; TOE = transoesophageal echocardiography.*

Importantly, this study also demonstrated the long-term safety of percutaneous PFO closure because repeat echocardiography at different time intervals beyond 10 years did not reveal any evidence of device dislocation, deformation, thrombosis, embolisation or pericardial effusion, which would indicate device-related erosion of adjacent structures. Favourable long-term echocardiographic features documented in this study were associated with even lower rates of recurrent TIA/CVI than reported previously.[4] This finding may be related to the higher proportion of patients undergoing balloon sizing, leading to more accurate device sizing and less residual shunt, rather than to the strategy of lifelong acetylsalicylic acid treatment despite successful closure.

This study also investigated the mechanism underlying moderate or greater residual shunt after closure, which was documented in 15 patients at different time points during follow-up. If TOE did not reveal the cause of residual shunting, pulmonary CTA was performed to document eventual arteriovenous malformation.

Using this protocol, we were able to determine the cause of significant residual shunting in almost three-quarters of the 15 patients. For the remaining patients with a residual shunt, we believe that small leakage, most likely at the level of the closure device, may have been visible only during a more vigorous Valsalva manoeuvre, typically better performed during TTE rather than during TOE. Although some residual shunts could have been closed by an additional closure device, this was not attempted because none of the patients experienced a recurrent thromboembolic event.

Study Limitations

This study has several limitations. Because of its single-centre and single-operator observational design, our findings cannot be generalised. The use of closure devices was not randomised, with the type of closure device selected by the interventional cardiologist and echocardiographer, with significant variations also in device availability. Furthermore, the patients were not randomly assigned to repeat echocardiography beyond the 6-month postintervention period because echocardiography was performed at the discretion of an individual patient's cardiologist or neurologist, and in agreement with the patient. Because several patients, in the absence of recurrent thromboembolic events, declined repeat echocardiography, the number of echocardiographic examinations at different time points after PFO closure is limited. Moreover, with such patient recruitment, selection bias cannot be excluded. Finally, the study design did not incorporate a randomised comparator group with medical therapy or surgical closure.

Conclusion

This study demonstrated high (≥90%) rates and persistent functional PFO closure beyond 10 years, independent of closure device. There was no device embolisation, thrombus formation or pericardial effusion. Thus, the study provides valuable insights into the durability, adequacy of closure and long-term safety of PFO devices, which is especially relevant for younger patients who will live with these implants for decades. Importantly, favourable echocardiographic findings were associated with very low rates of recurrent TIA and CVI. Using repeat TOE or pulmonary CTA, we further identified the cause of significant residual shunt in almost 75% of patients with a residual shunt, with the causes including device leakage, uncovered fenestration/atrial septal defect and pulmonary arteriovenous malformation. ❑

Clinical Perspective

- This echocardiographic study demonstrated high (≥90%) rates and persistent functional PFO closure independent of closure device, without late device embolisation, thrombus formation or pericardial effusion during an extended follow-up period of >10 years.
- Favourable echocardiographic features were associated with very low rates of recurrent TIA (0.11 per 100 patient-years) and CVI (0.06 per 100 patient-years), indicating the long-term clinical effectiveness and safety of the procedure.
- In very rare patients with moderate or greater residual shunt after percutaneous closure, leakage at the level of closure device, fenestration, atrial septal defect and pulmonary arteriovenous malformation should be kept in mind.
- Because none of the patients in this study experienced a recurrent thromboembolic event, the therapeutic implications of the findings warrant further investigation.

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