Short-Term Results of Percutaneous Closure of Patent Foramen Ovale Guided by Transoesophageal Echocardiography in Patients with Cryptogenic Stroke: A Retrospective Study

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Research Article

Keywords: patent foramen ovale, cryptogenic stroke, ultrasound foaming test, interventional therapy, transoesophageal echocardiography

Posted Date: September 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-916531/v1

Abstract

Background

Patent foramen ovale (PFO) is a risk factor for cryptogenic stroke (CS), and interventional therapy for PFO can reduce the recurrence rate of CS. However, interventional therapies are primarily guided by X-ray imaging, and regular postsurgical follow-up with transthoracic ultrasound foaming test (UFT) is rarely performed. Thus, this study aimed to assess the short-term (1 year) results of PFO occlusion guided by transoesophageal echocardiography (TEE) and the results of regular UFTs.

Methods

Clinical records, echocardiographic data, and UFT results of 27 patients who underwent interventional therapy for PFO and CS were retrospectively analysed. The patients were grouped according to their preoperative UFT results: group A (n = 4), small volume of right-to-left shunts; group B (n = 8), moderate volume of right-to-left shunts; and group C (n = 15), large volume of right-to-left shunts. All patients were treated using an Amplatzer occluder under TEE guidance. UFT follow-up was conducted regularly until 1 year post-surgery.

Results

No significant differences in preoperative clinical data, echocardiographic data, or operative time were noted between the groups ($P > 0.05$). The length of the PFO and the diameter of the occluder differed between the groups as follows: group A = group B < group C ($p < 0.05$). One year postoperatively, there was no stroke recurrence. Two patients in group C developed atrial arrhythmia, which improved after 3 months of antiarrhythmic treatment. The positive UFT rate gradually decreased postoperatively, and 50% of patients still had a positive UFT 11.75 months after surgery. The positive UFT rate 1 year postoperatively differed between the groups as follows: group A = group B < group C ($p = 0.010$). A preoperative large-volume shunt was negatively associated with a negative UFT rate 1 year postoperatively ($b=-2.118$, $RR = 0.120$, $p = 0.002$).

Conclusion

In patients with PFO and CS, interventional therapy guided by TEE led to excellent short-term (1 year) outcomes. The positive UFT rate gradually decreased within 1 year of surgery. Preoperatively, a large volume of right-to-left shunts and large occluders were two risk factors for positive UFT results after surgery. Further studies are required to clarify the relationship between positive UTF results postoperatively and stroke recurrence.

Background

The incidence of ischaemic stroke in China has been increasing annually, and despite extensive examination, in approximately 40% of patients with stroke the aetiology is still unclear, and this is referred to as cryptogenic stroke (CS) [1,2]. Studies have shown that patent foramen ovale (PFO) is an independent risk factor for CS, especially in patients younger than 60 years with atrial septal aneurysm or a large volume of right-to-left shunts [3,4]. Compared with pharmacological treatments, PFO interventional therapy can significantly reduce the recurrence rate of stroke [5,6]; therefore, methods of diagnosis and interventional therapies for PFO have been rapidly developed. The transthoracic ultrasound foaming test (UFT) is an important examination that significantly improves the detection rate of PFO [7]; however, currently, most PFO interventional therapies are still performed using radiography, which is associated with the risks of exposure to radiation. Furthermore, follow-up transthoracic UFT after surgery is rarely performed [4,6]. Therefore, this study was designed to assess the short-term (1 year) effects of PFO interventional therapy guided by transoesophageal echocardiography (TEE) and the results of regular transthoracic UFTs after surgery.

Methods

Patients

This retrospective study included data of 30 patients who underwent PFO interventional therapy from April 2019 to July 2020 at our hospital. The inclusion criteria were as follows: 1) a clear diagnosis of CS and PFO; 2) age < 60 years; and 3) transthoracic UFT performed strictly according to requirements (before surgery and at 3, 6, 9, and 12 months after surgery). The exclusion criteria were 1) severe organ dysfunction; 2) atrial fibrillation or atrial flutter diagnosed before surgery; or 3) other heart diseases requiring simultaneous surgical treatment. Of these 30 patients, 2 were excluded due to preoperative atrial fibrillation and 1 was excluded due to severe liver disease. After applying the exclusion criteria, 27 patients were finally included. This study was approved by the Hainan Medical University Clinic Institutional Review Board. Due to the retrospective design of this study, the need for obtaining patient informed consent was waived.

Transthoracic UFT

First, activated normal saline was prepared using two 10-mL syringes: the first syringe was used to draw 8 ml of normal saline and the other draw 1 mL of air and 1 mL of the patient’s blood sample. The syringes were connected to a three-way valve and their contents were rapidly injected back and forth to fully mix the blood, normal saline, and air to obtain 10 ml of activated normal saline [8,9]. Two syringes were prepared for each patient, each containing 10 ml of activated normal saline.

Second, while the patient was in the supine position, an apical four-chamber view was obtained using transthoracic echocardiography. One syringe of activated normal saline was rapidly injected through the elbow vein of the patient. If a microbubble entered the left atrium within 10 cardiac cycles, it was recognised as a positive result. Afterwards, the patients were asked to perform the Valsalva manoeuvre (thoracic pressure ≥ 40 mmHg) for more than 10 s. The other 10 mL of activated normal saline was rapidly injected through the elbow vein [10]. The number of microbubbles in the left atrium during 3 cardiac cycles was recorded, and the partial flow of PFO was graded as follows: no shunt, no microbubbles in the left atrium; small, 1–10 microbubbles in the left atrium; moderate, 11–25 microbubbles in the left atrium; and large, > 25 microbubbles in the left atrium [8,9].

Third, the patients were divided into three groups according to their transthoracic UFT results: group A: small-volume shunt group; group B: moderate-volume shunt group; and group C: large-volume shunt group.

Surgical methods

All surgeries were performed under general anaesthesia and guided by TEE. The length of the PFO was measured on the double vena cava section of the middle oesophagus, and an occluder was selected based on the results. The diameter of the occluder was equal to the length of the PFO + 10 mm. The right femoral vein was punctured, and the interventional track was established: right femoral vein – right atrium – PFO – left atrium. An Amplatzer occluder (Abbott Medical, Nathan Lane North Plymouth, MN, USA) was implanted along this track. After the occluder was released, the interventional catheter was removed, and the right femoral vein puncture point was pressed to stop bleeding. Finally, the patient returned to the general ward.

Follow-up

All patients were regularly treated with aspirin for 6 months (3–5 mg/kg/d). At 3, 6, 9, and 12 months postoperatively, and the patients returned to the hospital for transthoracic echocardiography, transthoracic UFT, chest radiography, and electrocardiography. All echocardiography and UFT results were evaluated by two doctors independently. If the reports of these doctors were inconsistent, the opinion of a third doctor was requested, and the opinion of the majority was the final data included in the analysis.

Data collection and processing

Preoperative data included the sex ratio, age, weight, height, co-morbidities, right ventricular diameter (RV), left atrial diameter (LA), main pulmonary artery diameter (PA), left ventricular end-diastolic diameter (LVEDD), and left ventricular ejection fraction (LVEF). The length of the PFO was measured using TEE during surgery.

Intraoperative data collected included the operative time and diameter of the occluder. Follow-up data collected included common postoperative complications (pericardial tamponade, occluder migration, and local vascular injury), stroke recurrence, atrial fibrillation, atrial flutter, and UFT results.

Statistical analysis

Continuous data are expressed as mean ± standard deviation (SD), while categorical variables are expressed as percentages. Between-group comparisons were performed using the one-way analysis of variance, Chi-square test, or Fisher's exact test, as appropriate.

The relationship between the UFT results and follow-up time was analysed by performing a life-table analysis, and factors influencing the postoperative UFT results were analysed by performing a Cox regression analysis. All statistical data were processed with SPSS version 19.0 (IBM SPSS, Armonk, NY, USA), and *p* values < 0.05 were considered to be statistically significant.

Results

Preoperative information

Group A included four patients, with a mean age of 42.45 ± 11.413 years; group B included eight patients, with a mean age of 45.12 ± 8.271 years; and group C included 15 patients, with a mean age of 39.67 ± 10.959 years. There were no significant differences in the sex ratio, age, weight, height, frequency of diabetes, hypertension, hyperlipidaemia, RV, LA, PA, LVEDD, and LVEF between the groups. The length of PFO differed between the groups as follows: group A = group B < group C (p = 0.002). The characteristics of the study population are presented in Tables 1 and 2.

Table 1
Clinical characteristics of the study population

	Group A (n = 4)	Group B (n = 8)	Group C (n = 15)	*p* value
Female sex	2 (50.0%)	5 (62.5%)	9 (60.0%)	0.917
Age (mean ± SD, years)	42.25 ± 11.413	45.13 ± 8.271	39.67 ± 10.959	0.488
Weight (mean ± SD, kg)	56.38 ± 6.129	53.06 ± 10.591	59.25 ± 15.217	0.566
Height (mean ± SD, cm)	158.50 ± 7.326	158.13 ± 8.967	160.93 ± 5.063	0.592
Diabetes	1 (25.00%)	1 (12.50%)	1 (6.67%)	0.590
Hypertension	1 (25.00%)	3 (37.50%)	4 (26.67%)	0.848
Hyperlipidaemia	1 (25.00%)	1 (12.50%)	0 (0)	0.203
SD, standard deviation.				

Table 2
Echocardiographic characteristics of the study population

	Group A (n = 4)	Group B (n = 8)	Group C (n = 15)	*p* value
RV (mm)	25.00 ± 2.160	19.88 ± 5.410	20.60 ± 4.881	0.211
LA (mm)	25.75 ± 1.500	27.50 ± 4.106	29.33 ± 4.320	0.251
PA (mm)	19.25 ± 1.258	21.25 ± 2.053	21.87 ± 3.182	0.249
LVEDD (mm)	45.50 ± 7.326	40.63 ± 4.897	40.60 ± 5.527	0.293
LVEF (%)	58.00 ± 9.557	65.75 ± 2.375	64.73 ± 6.193	0.104
Length of PFO	11.00 ± 4.243	10.87 ± 3.421	15.34 ± 2.006	0.002

RV, right ventricular diameter; LA, left atrial diameter; PA, main pulmonary artery diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; PFO, patent foramen ovale.

Perioperative data

All patients were successfully treated with PFO interventional therapy, and there was no incidence of perioperative acute pericardial tamponade, occluder migration, cardiac rupture, or malignant arrhythmia. No significant difference was found in the operative time between the groups ($p = 0.580$). Group C had a significantly larger occluder diameter than the other two groups ($p = 0.012$). The intraoperative data of the study population are presented in Table 3.

Table 3
Intraoperative data of the study population

	Group A (n = 4)	Group B (n = 8)	Group C (n = 15)	*p* value
Time (min)	40.25 ± 11.955	32.75 ± 10.580	32.67 ± 14.568	0.580
Occluder (mm)	19.25 ± 3.500[a]	20.63 ± 3.623[b]	24.07 ± 2.463[a,b]	0.012

Statistic comparisons: comparison between groups, [a] $p < 0.01$; [b] $p < 0.05$

Follow-up data

All patients in this study were followed up regularly for 1 year. There was no recurrence of stroke, new migraine, pericardial tamponade, occluder migration, occluder-related valve dysfunction, death, bleeding, or oesophageal perforation within 1 year after surgery. There was no arrhythmia in groups A and B. Two patients in group C developed atrial arrhythmias (alternating atrial fibrillation and atrial flutter) 3 months postoperatively. They were treated with amiodarone (200 mg/d) and recovered after 3 months.

All patients underwent UFT regularly after surgery. The residual shunt on the atrial septum was excluded using transthoracic echocardiography before UFT (Fig. 1). At 1 year after surgery, no patients in group A had a positive UFT (Fig. 2). One patient in group B had a positive UFT (Fig. 3), whereas 10 patients in group C still had positive UFTs (Fig. 3). The positive UFT rate 1 year postoperatively differed between groups as follows: group A = group B < group C (p = 0.010). The rate of positive UFT results during follow-up are presented in Table 4.

Table 4
Positive results of the ultrasound foaming test during follow-up

	Group A (n = 4)	**Group B (n = 8)**	**Group C (n = 15)**
Three months	2	7	15
Six months	1	4	14
Nine months	0	3	10
Twelve months	0	1	10

A life-table analysis showed that the positive UFT rate gradually decreased as the follow-up period increased (Fig. 4). In this study, 50% of the patients still had positive results at 11.75 months postoperatively. Cox regression analysis showed that the positive UFT rate in group C was higher than that in group A during the follow-up ($p = 0.002$) (Fig. 5). There was no significant difference in the positive UFT rate between groups A and B ($p = 0.233$). Moreover, a preoperative large-volume shunt was negatively associated with a negative UFT rate 1 year postoperatively (b=-2.118, RR = 0.120, $p = 0.002$). Age, sex, weight, height, RV, PA, LVEDD, and LA had no significant effect on the postoperative UFT results ($p > 0.05$).

Discussion

The foramen ovale is an important structure of the foetal heart that allows oxygenated blood to flow from the right atrium into the left atrium and ventricle, which then supplies blood and oxygen to the whole body [11]. After birth, with a decrease in pulmonary artery pressure and an increase in left atrial pressure, the foramen ovale closes spontaneously in approximately 75% of the population [12]. In the remaining population, the foramen ovale does not close, resulting in PFO [13,14]. Studies have shown that PFO is a risk factor for CS; hence, interventional therapy for PFO has been attempted for decades [15]. In addition, interventional therapy has shown better results than pharmacological treatments [5,6]. Currently, UFT is widely used as an important diagnostic tool for PFO [7]. However, reports on follow-up transthoracic UFT results after PFO interventional therapy are rare [4,6]. Therefore, this study was designed to assess the short-term effects of PFO interventional therapy guided by TEE and the results of transthoracic UFT after surgery.

The results of this study were as follows. 1) All patients were successfully treated with interventional therapy under TEE guidance, with no recurrent stroke, new migraine, pericardial tamponade, occluder migration, occluder-related valve dysfunction or death, bleeding, or oesophageal perforation within 1 year after surgery. These results suggest that PFO interventional therapy under TEE guidance is safe. Compared to traditional X-ray-guided surgery, TEE-guided surgery provides clearer surgical images, avoids the use of contrast agents, and avoids exposure to X-rays [16,17]. 2) The most common complications after PFO interventional therapy are recurrent stroke and atrial fibrillation [18,19]; however, in this study, no cases of recurrent stroke occurred within 1 year after surgery, and only two patients developed atrial arrhythmias (alternating atrial fibrillation and atrial flutter) 3 months postoperatively, which improved after 3 months of amiodarone (200 mg/d) therapy. This finding demonstrates that PFO interventional therapy guided by TEE can lead to satisfactory short-term results. 3) In this study, some patients still had positive UFT results 1 year after surgery, the majority of whom belonged to group C. Possible reasons for these findings are as follows: a) The Amplatzer occluder, which is used worldwide, was used in this study. It has a metal-braided mesh structure without a film on the surface. Therefore, it cannot prevent the passage of microthrombi and microbubbles. However, the occluder is gradually embedded in the intima, after release during surgery. Then, when the occluder is completely embedded, the microthrombi and microbubbles would be unable to pass through it, resulting in a negative UFT result [19,20]. The present study shows that there are individual differences in the process by which the occluder is embedded. Moreover, patients with a large volume of right-to-left shunts prior to surgery will have a longer embedding process; b) With an increase in the diameter of the occluder, the process by which the occluder is embedded in the intima is prolonged; hence, UFT positivity after surgery is observed in the long term. In order to reduce the duration of UFT positivity after surgery, an occluder with a small diameter should be selected, and the diameter of the occluder should be equal to the length of PFO + 10 mm.

Studies have shown that the recurrence rate of stroke after PFO occlusion in patients with CS is 2.0% [19], and the reason for this is still unclear. This study shows that some patients still have positive UFT results 1 year after PFO occlusion, and this implies that microthrombi and microbubbles can still be shunted from the right atrium to the left atrium through the PFO occluder. This may be a risk factor for stroke recurrence after surgery. Therefore, further prospective, randomised, large-scale, and long-term studies are required to clarify the changes of UFT after PFO occlusion and to verify the relationship between positive UTF results postoperatively and stroke recurrence.

Conclusions

In patients with PFO and CS, interventional therapy guided by TEE led to excellent short-term (1 year) outcomes. The positive UFT rate gradually decreased within 1 year after surgery. Preoperative large volumes of right-to-left shunts and a large occluder are two risk factors for positive UFT results after surgery. Further studies are required to clarify the relationship between positive UTF results postoperatively and stroke recurrence.

List Of Abbreviations

PFO
patent foramen ovale
CS
cryptogenic stroke
UFT
ultrasound foaming test
TEE
transoesophageal echocardiography
RV
right ventricular diameter
LA
left atrial diameter
PA
main pulmonary artery diameter
LVEDD
left ventricular end-diastolic diameter
LVEF
left ventricular ejection fraction
SD
standard deviation

Declarations

Ethics approval and consent to participate: This study was approved by the Hainan Medical University Clinic Institutional Review Board, and the need for patient consent was waived due to the retrospective study design. The protocol of this study was performed in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article and supplementary information files.

Competing interests: The authors declare that they have no competing interests to declare.

Funding: This work was supported by a grant from the 2018 medical and health research project of Hainan Province (grant number: 1801320114A2008). All of the transthoracic UFTs after surgery were paid by this funder.

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Author' contributions:

YG and ZS conceptualised and designed the study. YS and DZ provided administrative support. YZ and XW provided study materials or helped in recruiting patients. ZC and YS collected and assembled all data. YG and DZ analysed and interpreted the data. YG and ZS wrote the manuscript. All authors provided their final approval of the manuscript

Acknowledgements: Not applicable.

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Figures

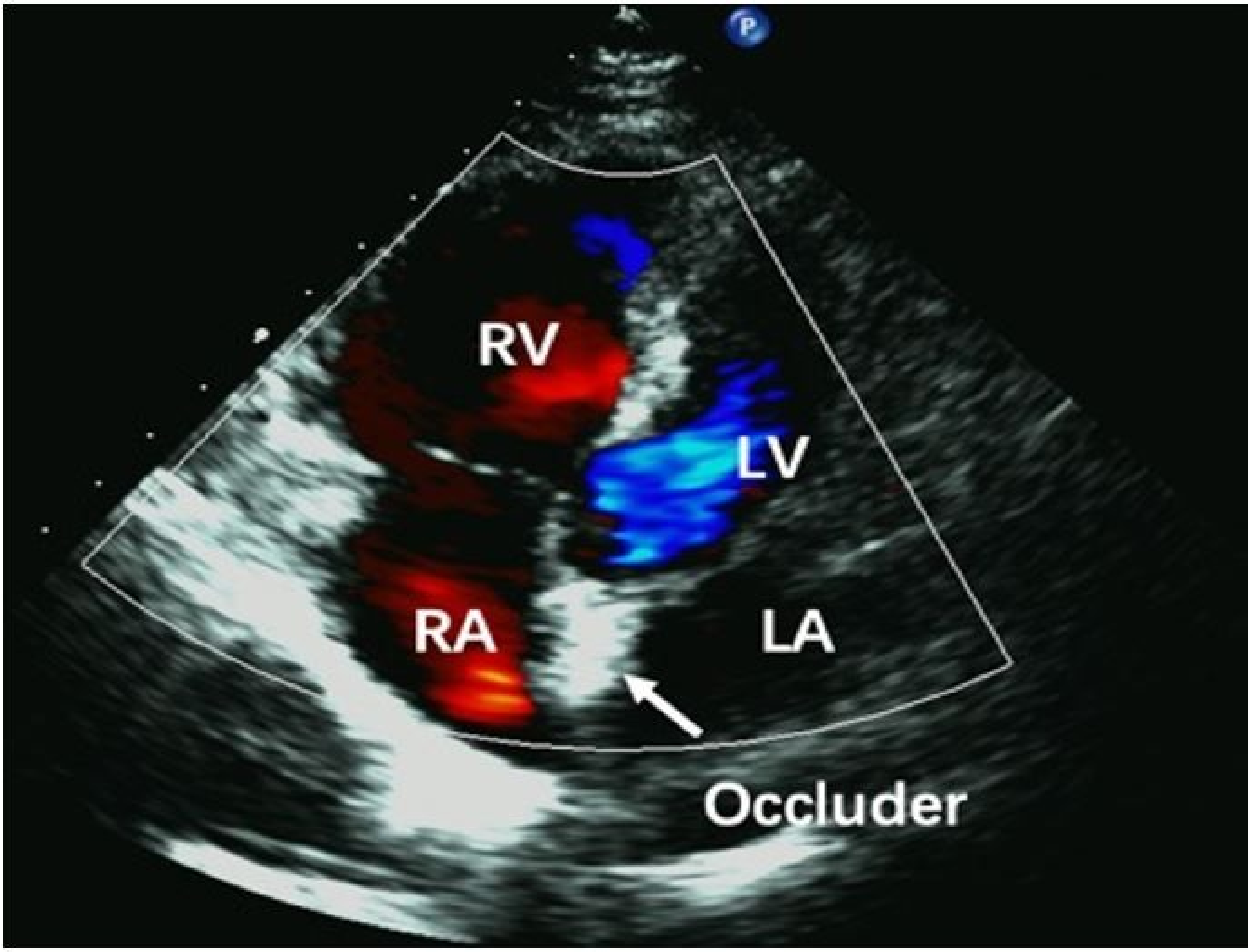

Figure 1

Blood flow image after PFO occlusion No residual shunt was noted between the LA and RA. LV, left ventricular; LA, left atrial; RV, right ventricular; RA, right atrial; PFO, patent foramen ovale

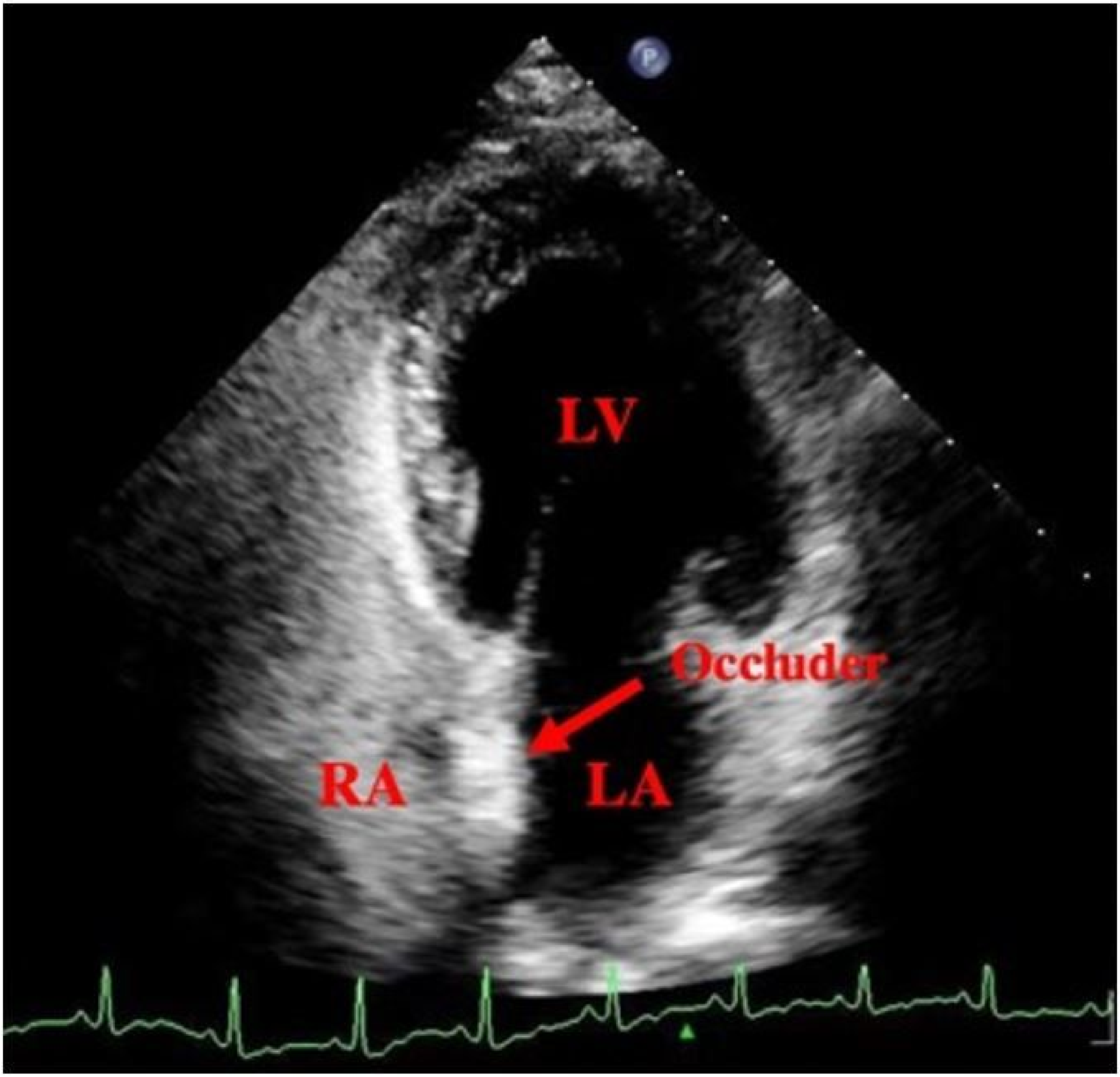

Figure 2

Negative transthoracic UFT result after PFO occlusion There was no microbubble in the LA. LV, left ventricular; RA, right atrial; LA, left atrial; PFO, patent foramen ovale; UFT, ultrasound foaming test

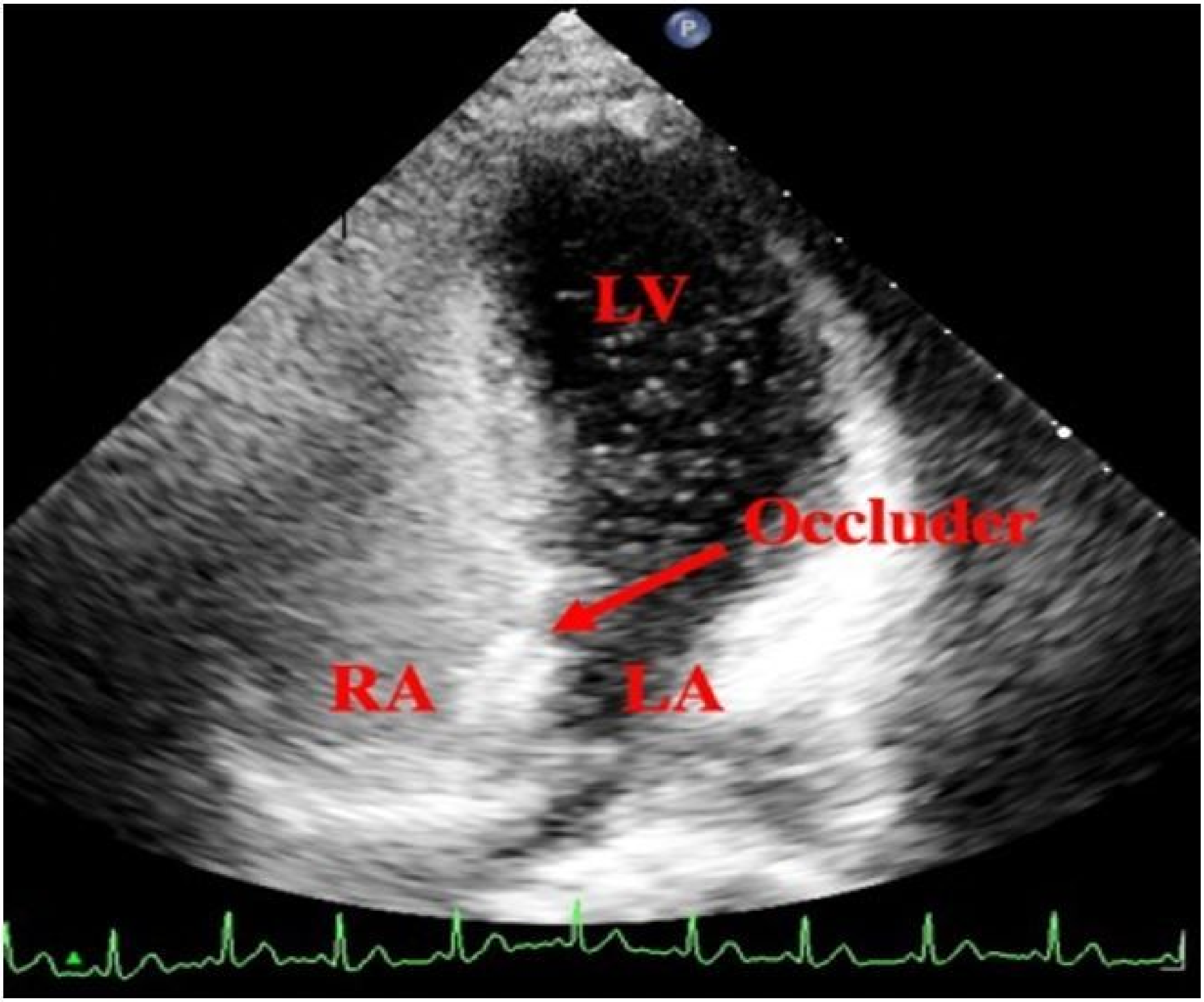

Figure 3

Positive transthoracic UFT result after PFO occlusion There were more than 25 microbubbles in the LA and LV. LV, left ventricular; RA, right atrial; LA, left atrial; PFO, patent foramen ovale; UFT, ultrasound foaming test

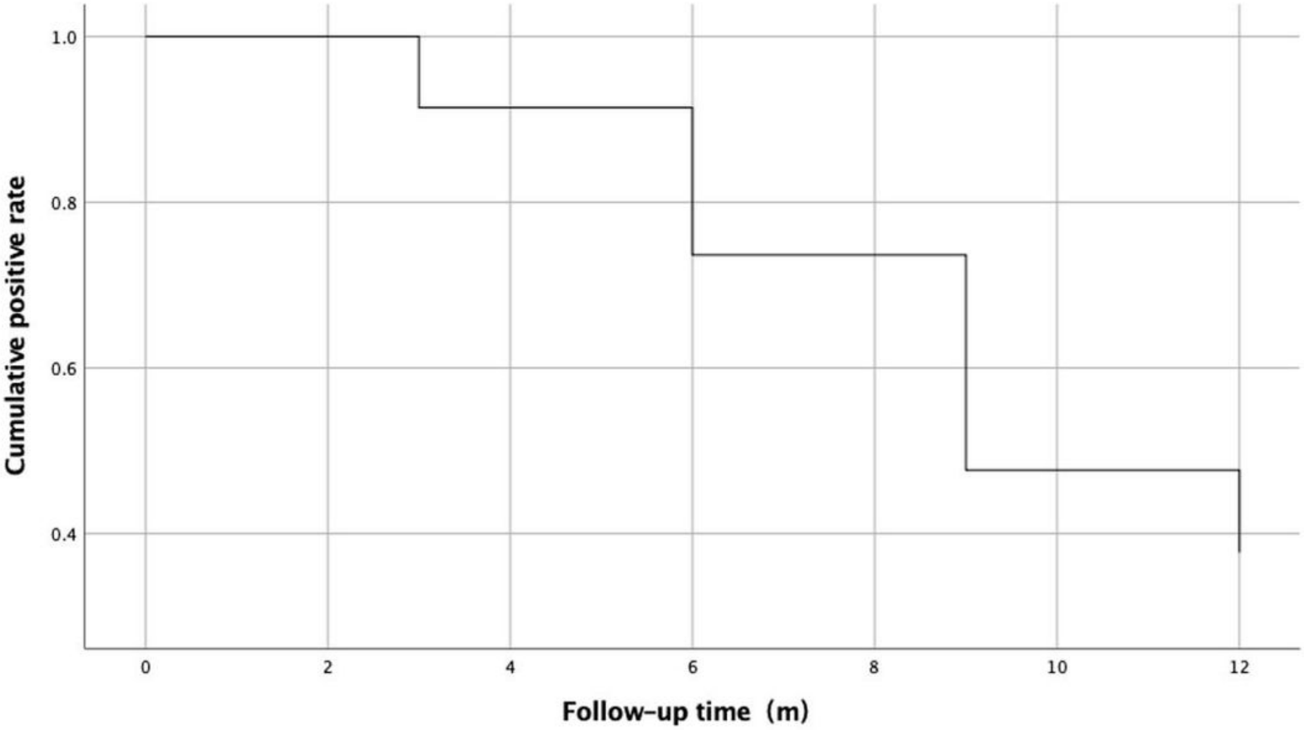

Figure 4

Life-table analysis: the cumulative positive UFT rate for all patients UFT, ultrasound foaming test

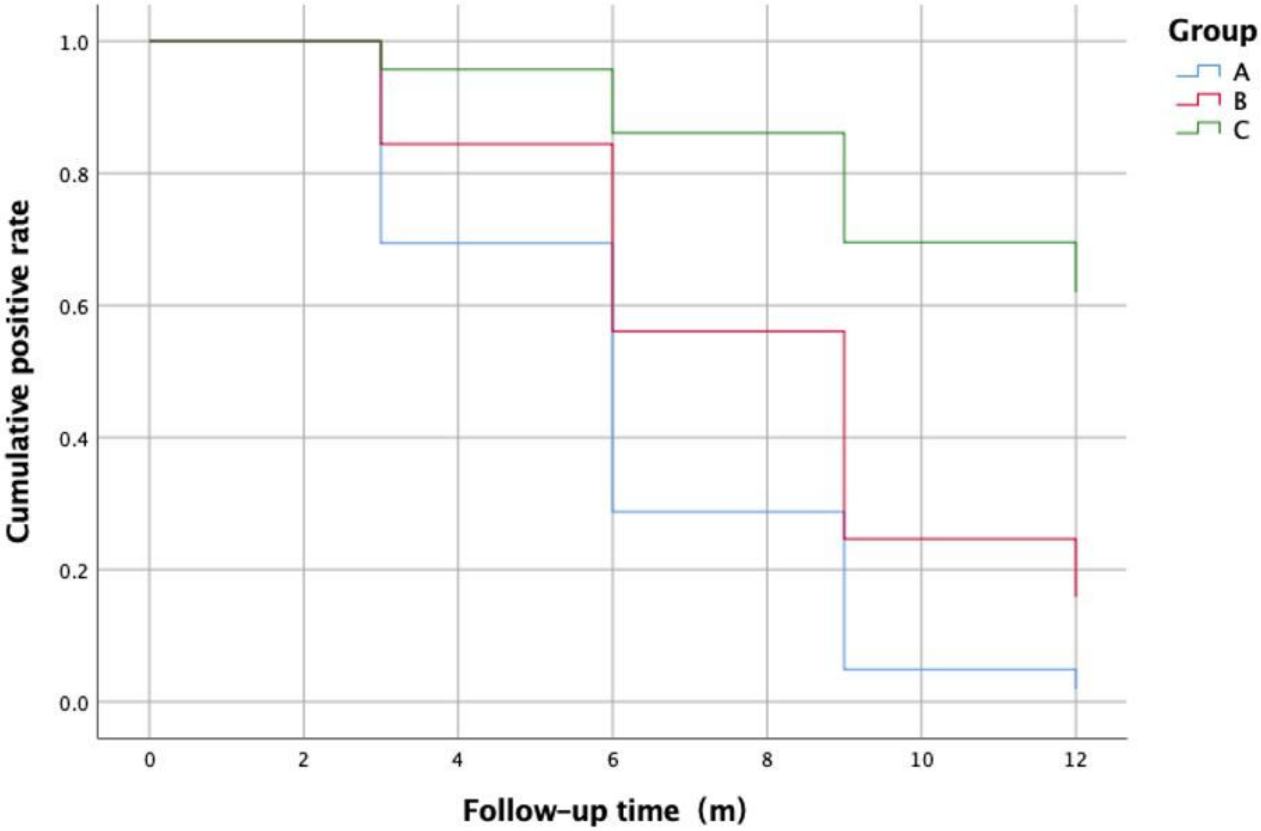

Figure 5

Cox regression analysis: the cumulative positive UFT rate for different groups UFT, ultrasound foaming test