Residual Shunt after Patent Foramen Ovale Device Closure in Patients With Cryptogenic Stroke: Serial Bubble Contrast Transesophageal Echocardiography Data

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Background: Percutaneous closure of patent foramen ovale (PFO) is an alternative option to medical treatment for secondary prevention for cryptogenic stroke (CS). Despite technical success of procedure, residual shunt (RS) which is a presumable cause for recurrent stroke is observed in some patients. We evaluated the RS with serial follow-up bubble contrast transesophageal echocardiography (BCTEE) after PFO closure. *Methods:* Among consecutive 47 CS patients who underwent PFO closure, a serial follow-up BCTEE at 3 and 9 months after the index procedure was completed in 38 patients (81%, 46 ± 10 years, 19 men). To evaluate the efficacy of PFO closure, the incidence of any and significant RS (≥ moderate) was assessed. *Results:* All PFO closure procedures were successful. The Amplatzer PFO Occluder (n = 19) or the Gore Septal Occluder (n = 19) were used. Any RS was observed in 13 (34%) and 10 patients (26%) at 3 and 9 months after the procedure. Significant RS was observed in 6 (16%) and 4 (11%) patients at 3- and 9-month follow-up BCTEE. Patients who were treated with the Gore Septal Occluder have a less incidence of any RS in 3 months, and any/significant RS in 3- and 9-month follow-up BCTEE without statistical significance. *Conclusions:* RS grade keeps decreasing after PFO closure, but it remains even after 9 months in some patients. Incomplete sealing of PFO should be taken into consideration in management of CS patients even after technically successful PFO closure.

Key Words: Patent foramen ovale—PFO closure—residual shunt—bubble contrast transesophageal echocardiography

Introduction

Patent foramen ovale (PFO) is found in about a quarter of general population[1] and is associated with paradoxical embolism potentially resulting in cryptogenic stroke (CS).[2,3] In patients with CS, PFO can be sealed with commercially available devices for secondary prevention; but, primary randomized trials have failed to prove a significant advantage of PFO closure over medical therapy.[4-6]

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Potential reasons include (1) investigators in those research focused mainly on clinical outcomes, but did not consider interventional results strictly; (2) follow-up duration was relatively short, up to 4 years; and (3) early discontinuation of antiplatelet agents after the index procedure might have been inappropriate. Meanwhile, recently published studies regarding long-term benefits of PFO closure and favorable outcomes of PFO closure with chronic concomitant antiplatelet therapy[7-9] raise a question for closure process after "successful" deployment of PFO closure device. In clinical practice, residual shunt (RS), which is a presumable cause for recurrent stroke, is observed in some patients despite technically successful device deployment.[10-13] However, little is known regarding shunt-sealing process after PFO device closure. We, hereby, report our serial evaluation data for RS after PFO device closure with bubble contrast transesophageal echocardiography (BCTEE) in real-world practice.

Subjects and Methods

Subjects

The current investigation analyzed the date from the Gil Medical Center, Gachon University College of Medicine PFO registry. Between March 2014 and February 2017, all consecutive 47 patients with CS were enrolled, when CS is defined as the brain infarction that is not attributable to a source of definite carotid or intracranial artery stenosis, atrial fibrillation, and thrombus/atheromatous plaque at the aortic arch despite a standard vascular, cardiac, and serologic evaluation. In all participants, PFO was documented by BCTEE. PFO closure was determined according to the heart-brain team's discretion (the team consisted of an interventional cardiologist, an echocardiographer cardiologist, a neurologist, and a radiologist) based on clinical data, echocardiographic findings, and patients' preference. The Gore Septal Occluder (WL Gore & Associates, Inc., Newark, DE) (n = 19) and the Amplatzer PFO occluder (St. Jude Medical, Inc. St.Paul, MN) (n = 19) were used at the operator's discretion. The Occlutec PFO occluder was used in one patient who were excluded from the analysis (Fig 1). The Institutional Review Board of Gachon University Gil Medical Center approved this study and all patients provided written informed consent prior to enrollment.

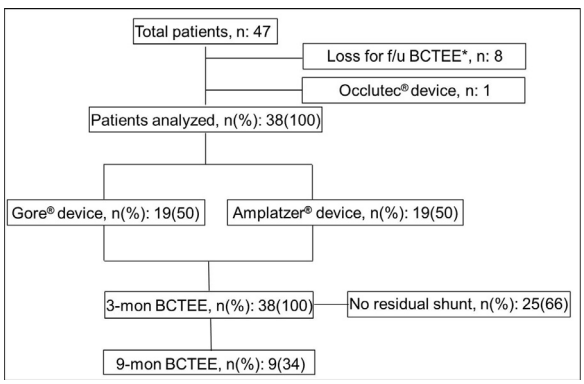

Figure 1. *Diagram for detailed follow-up of patients.*
*BCTEE: Bubble contrast transesophageal echocardiography.

Assessment of Patent Foramen Ovale Shunt Grade and Atrial Septal Aneurysm

PFO shunt size was assessed in all patients by BCTEE during the Valsalva maneuver after careful educations and explanations.[14] Shunt was defined as presence of aerated saline contrast bubbles in the left atrium within 3 cardiac cycles of right atrial opacification. Degrees of shunting were defined as "mild" if 3-9 contrast bubbles appeared, "moderate" if 10-30 contrast bubbles appeared, and "severe" if more than 30 contrast bubbles appeared in the left atrium as in previous research.[10,13,15,16] Shunt at rest was defined as the appearance of agitated saline contrast in the left atrium within 3 cardiac cycles of right atrial opacification with normal respiration or color Doppler noted shunt flow. Atrial septal aneurysm (ASA) was defined as interatrial septal excursion during the cardiac cycle of ≥10 mm from midline on transesophageal echocardiography (TEE).[17]

Patent Foramen Ovale Device Closure and Postprocedural Medication

The closure procedure was performed under general anesthesia. After achieving femoral venous access, the PFO was crossed with a 5F multipurpose catheter, which was advanced into the left upper pulmonary vein and then exchanged over a 0.035 inch J-tipped stiff guidewire for an 8F or 9F guiding sheath. Procedural anticoagulation was initiated with 5000 units of intravenous heparin. After then additional heparin was administrated throughout procedure to maintain an activated clotting time of ≥250 seconds. Device size was selected based on TEE measurements of the distance between the PFO and the aortic root. Device was implanted according to previously described methods.[18,19] TEE was used to facilitate device implantation and confirmation of its successful positioning. Procedural success was defined device implantation without any complication. Recommended antiplatelet therapy following the procedure included aspirin 100 mg daily and clopidogrel 75 mg daily for at least 6 months. After that, aspirin monotherapy was maintained in all patients.

Evaluation for Residual Shunt After the Index Procedure

We performed the BCTEE at baseline (before the index procedure to diagnose PFO), 3- and 9-month after the index procedure for evaluation of RS. The severity of RS was graded semiquantitatively according to the number of microbubbles identified in the left atrium as previously

mentioned. Depending on these results, we defined complete closure as procedural success with no RS by BCTEE and effective closure as result with none or mild, respectively. Significant RS was defined as moderate to severe ones.

Statistical Analysis

Data are presented as the mean and standard deviation and compared using 2-sample *t* test for continuous variables. Discrete variables are expressed as absolute values and percentages. Categorical variables were compared using the chi-square test and Fisher's exact test, as appropriate. All test were 2-sided with statistical significance accepted at the *P* value <.05. Statistical analyses were performed with IBM SPSS Statistics software version 20 (Chicago, IL).

Results

Patients' Characteristics

The demographic data of patients are given in Table 1. All 47 patients (mean age, 46 ± 10) were enrolled in this study. Out of 47 patients, 8 patients (17%) did not undergo follow-up BCTEE. One patient treated with Occlutec device was excluded from analysis to compare outcomes between the 2 devices (Gore and Amplatzer) (Fig 1). Thus, all 38 patients' data were analyzed. Baseline clinical and TEE characteristics were similar in the 2 groups. Strokes were main indication for PFO closure (n = 33, 87%). Risk of Paradoxical Embolism Score, which was developed to predict the probability of presence of PFO in CS patients[20] was relatively high (6.5 ± 1.3). The presence of shunt at rest and ASA was rare but did not differ in 2 groups (Table 1).

Procedural Characteristics

Detailed procedural data on PFO closure are given in Table 2. All PFO closure procedures were successful. The Amplatzer PFO occluder and the GORE Septal occluder were implanted in an equal number of patients (n = 19, 50%). The most commonly used device size was 25 mm in both groups (n = 15, 40% vs. n = 13, 34%). There were no procedure-related complications including cardiovascular death, new-onset atrial fibrillation, arteriovenous fistula, left atrial wall perforation, bleeding requiring transfusion, or device migration after PFO closure.

Serial Evaluation Data for Residual Shunt

Figure 1 shows serial BCTEE data. The Gore device and the Amplatzer device was used in 19 patients (50%) each. Patients without RS in 3-month BCTEE (25 patients, 66%) were considered that PFO was completely sealed and did not undergo 9-month BCTEE. On the other hand, any RS were observed in 13 (34%) and 10 (26%) patients at 3 and 9 months (Fig 2A). Significant RS were observed in 6 (16%) and 4 (11%) of patients at 3 and 9 months, respectively (Fig 2B). The Gore device group patients tend to show any (26% vs. 42% at 3 months and 26% vs. 26% at 9 months) or significant RS (0% vs. 32% at 3 months and 0% vs. 21% at 9 months) less frequently compared with the Amplatzer device group; however, *P* value did not reach statistically significant zone, presumably for small number of patients (Table 2). Key cases from our cohort are presented in Figure 3.

Clinical Outcomes During Follow-up Period

During follow-up period, only 1 cerebrovascular event occurred in Amplatzer group (0% vs. 5%, *P* = 1.000) (Table 2).

Table 1. *Baseline clinical and transesophageal echocardiographic characteristics*

	All (n = 38)	Gore septal uccluder (n = 19)	Amplatzer PFO occluder (n = 19)	*P* value
Age, years	46 ± 10	45 ± 11	48 ± 9	.479
Male, n (%)	19 (50)	9 (47)	10 (53)	1.000
BMI, kg/m^2	25 ± 4	25 ± 4	25 ± 4	.778
Hypertension, n (%)	9 (24)	3 (16)	6 (32)	.447
Diabetes mellitus, n (%)	1 (3)	0 (0)	1 (5)	1.000
Dyslipidemia, n (%)	14 (37)	10 (53)	4 (21)	.091
Smoker, n (%)	14 (37)	7 (37)	7 (37)	1.000
Coronary artery disease, n (%)	0	0	1 (1)	1.00
Indication for closure				
stroke, n (%)	33 (87)	16 (84)	17 (90)	.631
recurrent TIA, n (%)	5 (13)	3 (16)	2 (11)	1.000
RoPE score	6.5 ± 1.3	6.5 ± 1.2	6.4 ± 1.4	.903
Shunt at rest, n (%)	3 (8)	2 (11)	1 (7)	1.000
Atrial septal aneurysm, n (%)	2 (5)	0 (0)	2 (11)	.486

ASA, atrial septal aneurysm; BMI, body mass index, , RoPE score, risk of paradoxical embolism score; ; TIA, transient ischemic attack.

Table 2. *Procedural characteristics and clinical outcomes during follow-up period*

	All (n = 38)	Gore septal occluder (n = 19)	Amplatzer PFO occluder (n = 19)	*P* value
Device size				
18 mm		0	3 (8)	
25 mm		13 (34)	15 (40)	
30 mm		6 (16)	1 (3)	
Complication, n (%)	0			
Cardiovascular death	0			
New-onset atrial fibrillation	0			
Arteriovenous fistula	0			
LA wall perforation, n (%)	0			
Bleeding requiring transfusion	0			
Device migration	0			
Procedural outcomes				
Complete closure, (%)	28 (74)	14 (74)	14 (74)	1.000
Effective closure, (%)	34 (90)	19 (100)	15 (79)	.105
Clinical outcomes				
Cerebrovascular events, n (%)	0	0	1 (5)	1.000
stroke, n (%)	0	0	1 (5)	1.000
TIA, n (%)	0	0	0	
Cardiovascular death, n (%)	0	0	0	

TIA, transient ischemic attack.

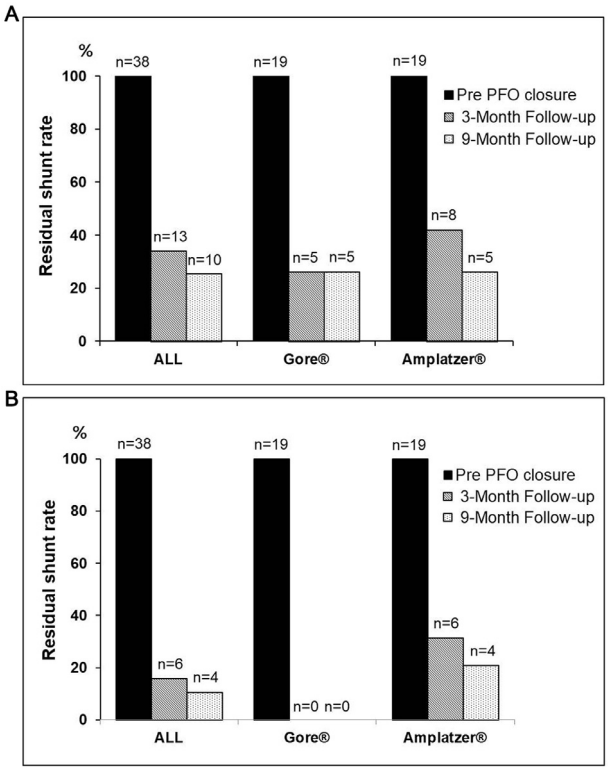

Figure 2. *Bubble contrast transesophageal echocardiography follow-up data. (A) About a quarter of patients still have residual shunt of any degree even*
9-months after the technically successful patent foramen ovale (PFO) device implantation. The Gore device tends to be sealed earlier than the Amplatzer device without statistical significance. (B) It is remarkable that significant shunt [≥ moderate] persists even 9-months after the index procedure in some patients.

Discussion

Core Findings

Principal findings of this study are: (1) RS grade keeps decreasing over time after PFO device closure but, (2) any or significant RS remains even 9 months after the index procedure in a considerable number of patients. The strong point of this investigation is that serial thorough evaluations of RS were performed in all subjects with BCTEE which renders better image of the left atrium and PFO closed with device than transthoracic echocardiography.[16] Therefore, the accuracy and sensitivity of shunt evaluation are far more improved in this study. Although clinical implication of RS cannot be fully determined currently, our real-world data raise important questions discussed below.

Unanswered Question # 1: Procedural Soundness—Is What We Consider a "Success" the "Real Success"?

Commercially available devices are widely used to close the PFO with technical "success." However, high prevalence of RS in the current investigation suggests the "successful" device deployment does not guarantee complete sealing of the culprit PFO. In previous landmark randomized studies (the PC, the RESPECT and the CLOSURE I trial), investigators performed only single BCTEE at 6 months after the procedure, and reported 86.1%-95.9% of cases were "success." However, considering the results of the current investigation, we authors are skeptical of the arbitrary definition of the "success" [ie mild RS is "success"] of the procedure. RS is associated with re-event of stroke[12]; in fact, some CS patients in device-

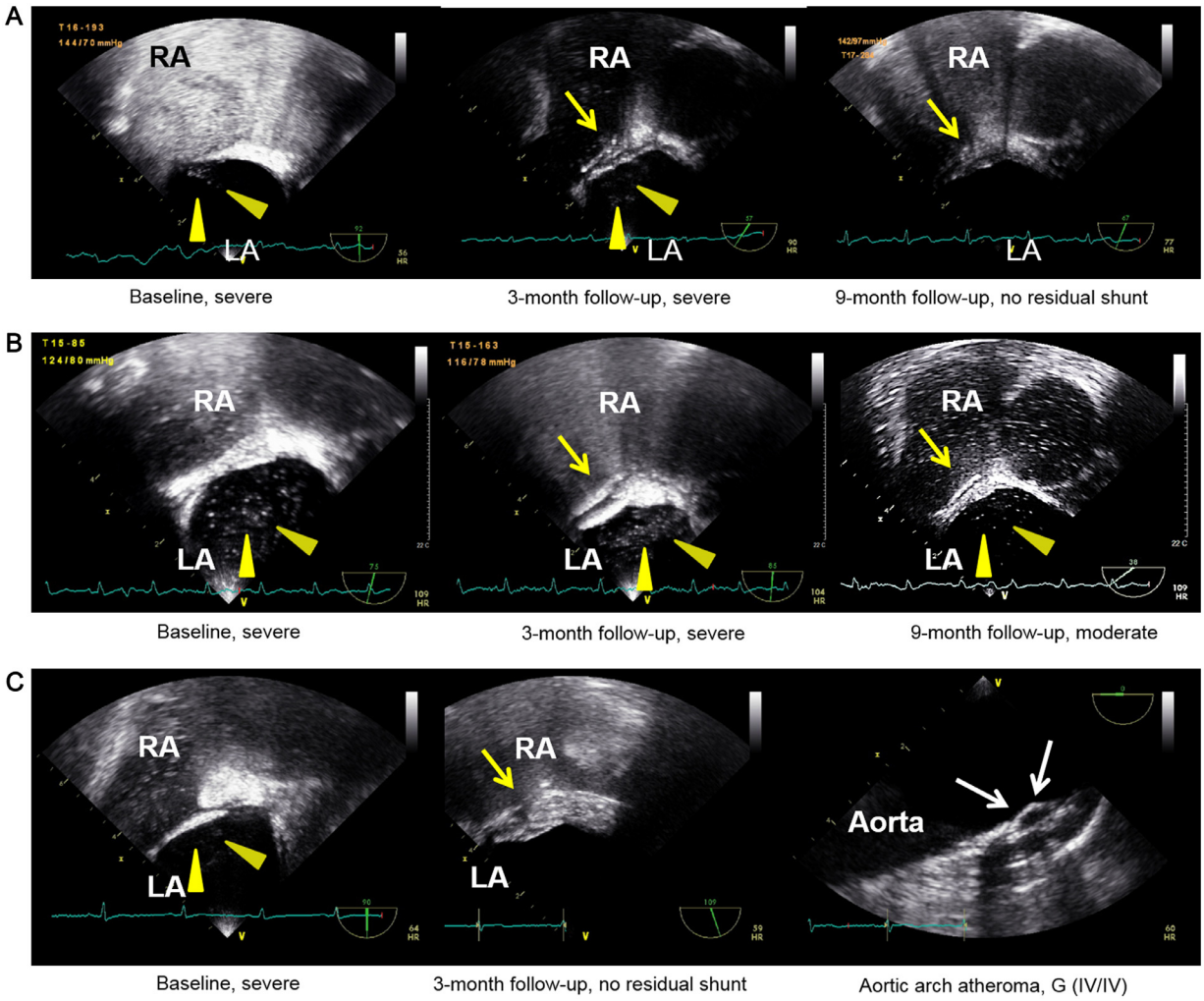

Figure 3. *Key cases. (A) A 63-year-old male with cryptogenic stroke (CS). At baseline, severe shunt (see arrow heads, agitated saline bubbles) resulting from patent foramen ovale (PFO) was observed in bubble contrast transesophageal echocardiography (BCTEE). In 3-month follow-up BCTEE after implantation of the Gore device (arrow), many saline bubbles (arrow heads) are still observed in the left atrium (LA) suggesting a significant shunt of severe degree. However, in 9-month follow-up, no shunt remained and PFO was completely sealed. (B). A 64-year-old male with CS and severe shunt via PFO underwent PFO device implantation with the Gore device still showed severe and moderate shunt in 3- and 9-month follow-up BCTEE, respectively. (C) A 60-year-old male with ischemic stroke and large shunt (arrow heads) resulting from PFO was treated with the Gore device (yellow arrow). In 3-month follow-up BCTEE, PFO was completely sealed. Strikingly, this patient experience recurrent stroke 3.5 month after the index procedure. There is an atheroma of G (IV/V), which means atheroma protruding ≥5 mm at the aortic arch without mobile component or ulceration, in this patient.*

closure arm experienced recurrent stroke in those trials[4-6] including recently published long-term follow-up data,[7] and even under chronic concomitant antiplatelet therapy.[8,9] Therefore, even mild RS, which has been labeled as a "success," is not always the "success" and we suggest that "small" RS remaining after so-called "successful" procedures may not be clinically "small". In our cohort, there are patients without any decrease in shunt even 9 months after device implantation. Vitarelli et al[16] also reported that incomplete closure of the PFO in about 17% of patients at 12 months after the procedure.

We observed a trend of earlier sealing of shunt in Gore-device implanted patients. The phenomenon failed to show statistical significance presumably for small number of patients; but we think there would be potential role of the devices,[16] because Gore-device shows less bulky profile and might be easy to be sealed with more rapid endothelialization.

Unanswered Question # 2: Postprocedural Management

Another issue is the optimal duration of blood-thinning therapy after the index procedure. Complete endothelialization of device-deployed PFO is known to be completed in 1 month in animal experiment (Supplemental Figure I, with courtesy of the Gore); however, this phenomenon has not been universally proven in human. Our data suggest complete sealing of the PFO occlusion site is not achieved in about quarter of patients even 9 months after the index procedure. Previous investigators of the

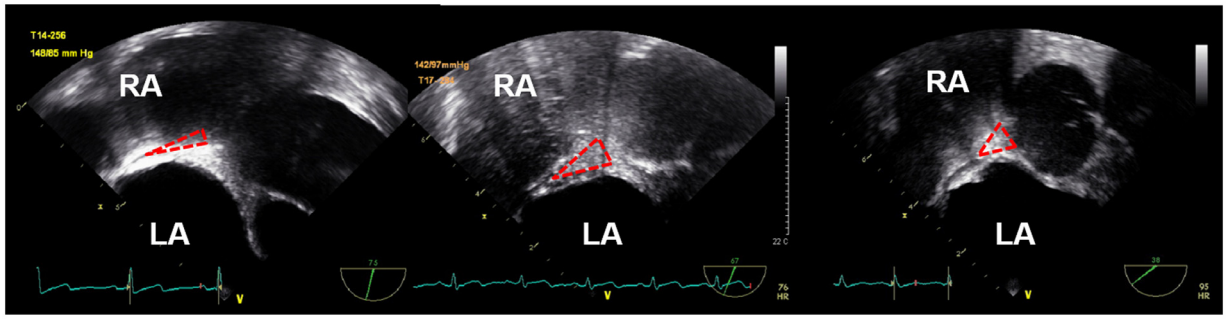

Figure 4. *Different morphological features of patent foramen ovale closure site.*

landmark trials[4-6] did not perform serial assessment of shunt-sealing process. However, complete sealing of the PFO might fail in some patient probably for incomplete endothelialization. Therefore, meticulous RS evaluation might be required, and a requirement for chronic antiplatelet or anticoagulation therapy needs to be customized. We do not reckon that PFO occlusion is meaningless even in patients with persistent RS, because the procedure—at least reduces the thrombotic burden passing through a shunt. However, patients having a CS for a presumed paradoxical embolism via a PFO are usually young and otherwise healthy; thus preventing recurrence is of paramount importance, and the "fire and forget" is no good strategy considering the result of this study. In addition, increased risk of atrial fibrillation is reported after PFO occlusion[8,9]; and after that, CS becomes "not cryptogenic" any more and strategic alteration in secondary prevention for stroke is mandatory. Furthermore, considering data supporting benefits of persistent antiplatelet therapy after device implantation,[8,9] universal discontinuation of the drugs 6 months after the procedure should be reconsidered. Therefore, long-term individualized treatment plan is essential.

Unanswered Question # 3: Patient Selection for the Patent Foramen Ovale Occlusion

Let us introduce one of our patient who had CS but was excluded from our study for failure of fulfillment of the enroll criteria. The patient had large shunt resulting from PFO; and thus, we decided to close PFO despite an atheroma at the aortic arch which might be another or the "real" contributor of ischemic stroke. He experienced recurrent stroke after complete closure of PFO in follow-up BCTEE (Fig 3C). This case raises fundamental question for patient selection issue for PFO occlusion. Currently, we cannot determine the cause of the initial cerebral infarct of the patient. However, the large PFO might have been an innocent bystander, not a smoking gun. Although the prevalence of a PFO is much higher in CS than in nonstroke patients, the presence of a PFO and the size of the right-left shunt have not been clearly linked to an ischemic event. Although anatomical characteristics of the culprit PFO not currently well established, recently published study by Mas et al[8] suggests that patients with specific echocardiographic features (ie ASA[21] or large shunt[22]) are prone to thrombotic complication. Therefore, more investigation should be performed regarding patient selection issue for PFO occlusion with consideration of clinical situation, anatomic characteristics, and cardiac hemodynamic information.[23]

Limitations

First, this is a single center observational study with all the inherent limitations of this study design. Second, the number of patients was small: moreover, BCTEE were not performed in 17% of enrolled patients. On the other hand, it shows the real world practice in PFO device-closure follow-up. BCTEE is a semi-invasive procedure, and thus, some patients were reluctant to take the exam repeatedly. However, based on the result of this study, BCTEE follow-up after 9 months (or even later follow-up) should be considered to assess the interventional outcomes which might alter patient-management strategy even after successful device deployment. According to the recently published serial TEE study,[16] the time of complete closure after device implantation for a PFO was more dependent on morphological features of PFO than on the type of the device. Although we could observe some typical cases (Fig 4), we did not thoroughly assess the influence of morphological features of PFO on closure time in this cohort.

Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.10.006.

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