Transcatheter Patent Foramen Ovale Closure Guided Only by Transesophageal Echocardiography Without fluoroscopy

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Research

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Abstract

Background

Standby of transesophageal echocardiography (TEE) is necessary for any PFO closure in case of some cases with complicated anatomy of patent foramen ovale (PFO). The safety and effectiveness of Transcatheter PFO closure guided only by TEE navigation without fluoroscopy is unclear.

Methods

From 2017.06 to 2019.11, we included 38 patients who were recommended for PFO closure by the department of neurology at our hospital. The procedure was performed in a regular operating room by TEE navigation without fluoroscopy. Follow-up was given at 1st month, 3rd month, 6th month, 1st year and 2nd year after operation for each patient.

Results

All 38 patients were successfully performed PFO-closure guided by TEE. Procedural and intrahospital survival was 100%. Survival after a mean follow-up of 17.1±1.6months was 100%. "Catheter in sheath" technique was adopted in 16 cases. After the procedure, all 28 migraines with aura alleviated at different degree. All 10 patients suffering from pre-operational cryptogenic stroke survived and showed no evidence for recurrence of stroke (fatal or non-fatal), peripheral embolism or transient ischemic attack during follow-up. No serious adverse events in the PFO closure procedure and during the follow-up period.

Conclusion

First clinical experiences showed that percutaneous TEE guided PFO closure is safe and effective and might be promoted.

Introduction

Patent foramen ovale (PFO), a remnant of fetal anatomy, is associated with neurological events (such as cryptogenic stroke, transient ischemic attack[1], migraine with aura[2] among other clinical manifestations) because the permanent or temporary open statue of foramen ovale may allow blood from the right atrium to communicate directly with the blood in left atrium. This communication may cause “paradoxical emboli”, where thrombi originating from a vein pass through the foramen ovale into the systemic arterial circulation, causing cerebral or other systemic thromboembolic infarction [3]. The prevalence of PFO is approximately 25%[4] in the adult population. If patients with neurological events benefit from PFO closure is discussed controversially. Some studies showed that patients with cryptogenic stroke have a decreased risk of recurrent stroke and patients[5] suffering from migraine with aura experience a remission of migraine[6] after PFO closure. Interventional PFO closure is usually performed using fluoroscopy and transesophageal echocardiography (TEE) guidance. Some experienced interventional cardiologists even perform PFO closure using fluoroscopy navigation only[7, 8]. However,

standby of TEE is necessary for any PFO closure in case of some cases with complicated anatomy of PFO. As standard interventional PFO closure is fluoroscopy-guided, we evaluated interventional PFO closure guided by TEE only with considerable experience in atrial septal defect closure[9], our center performed PFO-closure in patients following the recommendation of a neurologist recommendation of closure.

Patient Selection And Methods

From 2017.06 to 2019.11, we included 38 patients who were recommended for PFO closure by the department of neurology at our hospital. 26 females and 12 males suffered from migraine with aura or cryptogenic stroke in the presence of a PFO. Age ranged from 9 to 57 years with a mean age of 36.2 ± 14.4 years. The patients who were recommended for PFO closure were enrolled by the criteria:

For migraine with aura, the patients were diagnosed by neurologists according to the criteria of the International Headache Society (2nd edition)[10]. For cryptogenic stroke or transient ischemic attack (TIA), the patients were diagnosed by neurologists with clinical and/or radiologically evidence.

For confirmation of a PFO, the patients were first screened by transcranial ultrasound for a right-to-left shunt. Next, patients were sent to transthoracic echocardiography (TTE) for advanced PFO evaluation: 1. confirmation of PFO; 2. ≥medium right-to-left shunt was detected (Right-to-left shunting, RLS, was detected with or without the Valsalva maneuver and > 10 microbubbles were detected in left atrium[11]).

Exclusive criteria: patients with psychiatric, neurodegenerative, inflammatory, infective diseases, pregnancy or contraindication to antiplatelet therapy were excluded. More patients baseline characters are described in Table 1.

Table 1
Baseline characteristics

Variable	Value
Total number	38
Female/male	26/12
Age(years)	36.2 ± 13.4(9–57)
Weight(kg)	56.1 ± 12.7(29–75)
Height(cm)	161.4 ± 10.6 (138–178)
Arrhythmia (IRBBB)	4(10.5%)
Migraine with aura	28(73.7%)
Additional migraine without aura	16(57.1%)
Other headache history	4(14.3%)
Mood disorder	4(14.3%)
Unresponsive to two medication	26(92.9%)
Cryptogenetic stroke	10(26.3%)
TIA	4(40%)
Multiple strokes	2(20%)
Migraine	2(20%)
Echocardiographic variable	
With ASA	4(10.5%)
Hypermobile septum	6(15.8%)
Large PFO	2(5.3%)
RLS > 2 grade after Valsalva	26(68.4%)
Values are mean ± standard deviation.	
IRBBB: Incomplete Right Bundle Branch Block; TIA: transient ischemic attack; ASA: atrial septal aneurysm; PFO: Patent foramen ovale.	

All procedures were under institutional guidelines and were approved by the institutional review committee. Study approval was obtained from the Committee on Clinical Applications at the Second Xiangya Hospital and informed consent was obtained from the patients or patients' parents (< 18 years old).

Procedure

The procedure was performed in a regular operating room by TEE navigation without fluoroscopy. All patients with supine position were TEE re-evaluated before the procedure. The main purpose was to reassure the PFO and provide device selection basis. When the re-evaluation confirmed the procedure, patients were given general anesthesia and routine sterilization. After puncture of the femoral vein, we inserted a 5 French sheath and advanced a 0.035-inch J-tipped stiff wire (Terumo Medical Corporation, Somerset, NJ, USA) into the superior vena cava with TEE monitoring. Heparin was given at a dose of 100 IU/kg and antibiotic prophylaxis was administered. With the J-tip wire in the superior vena cava, we retract the vascular sheath and enlarged the skin access according to the delivery sheath size. Then, we advanced the delivery sheath (Shanghai Shape Memory Alloy Co. Ltd., Shanghai, China) along the wire to the orifice of the inferior vena cava. With the tip of the delivery sheath in the orifice of the inferior vena cava, we retracted the tip of the inner sheath from the delivery sheath. Thereby, the right atrium was protected from the sharp tip of the inner sheath and the delivery sheath was delivered to the superior vena cava. Next, the tip of the delivery sheath was retracted and advanced into the right atrium. Then the wire and inner sheath were removed. Identifying a hollow sheath in the TEE, we slightly torqued the delivery sheath for the best angle, i.e. the angle where the tip of delivery sheath pointed directly towards the PFO. Usually, the sheath would approach the PFO or directly pass the PFO. Then we advanced the delivery sheath into the middle of the left atrium. If the tip of the delivery sheath and PFO could not be identified in the same plane in TEE because of the PFO maybe not in the best position of the atrial septum, then we used a so-called "catheter in sheath" technique to get through PFO. Then the AMPLATZER® PFO Occluder device (AGA Medical Corp, Plymouth, MN, USA) would be advanced into the left atrium and deployed in the PFO (Fig. 1).

Device selection criteria 1. Size of occluder was determined by the weak part of PFO zone because the device should cover the whole weak part; 2. If PFO combined with atrial septal aneurysm, the size of occluder was determined by the diameter of aneurysm.

“Catheter in sheath” technique Firstly, the delivery sheath should be the best angle approached to the atrial septum. A 5 Fr MPA 2 diagnostic catheter (Cordis, Johnson & Johnson, Warren, NJ, USA) and a straight stiff wire in it were put in the delivery sheath. Then the tip of the catheter could be torqued out of the delivery sheath and got the best approach to PFO with TEE probe rotating to detect PFO. If the tip of the catheter got closed to but not through the PFO, then the straight stiff wire could be advanced in the PFO. (Fig. 2)

Follow-up

Aspirin (3 mg/kg/day for children and 1 pill/day for an adult) was routinely administered for six months after the procedure. A contrast TEE at 3 months after discharge was scheduled to assess any residual shunting in basal condition and after Valsalva maneuver. A second TEE was recommended at 6 months

in case of the residual shunt as well as device erosion, migration or thrombosis. Neurologists evaluated patients with any recurrent neurologic symptoms and computed tomography (CT) or magnetic resonance (MR) was recommended for any suspicious new ischemic event. For migraine patients, the neurologist reviewed the headache diary and assessed disability due to migraine, quality of life, and depression by Migraine Disability Assessment Questionnaire (MIDAS)[12], Quality of Life Questionnaire SF12v2[13], and the Beck Depression Inventory (BDI)[14] at respectively before operation and at 1st month, 3rd month, 6th month after operation. Ordinary follow-up was given at 1st month, 3rd month, 6th month, 1st year and 2nd year after operation for each patient.

Statistical Analysis

SPSS 25.0 (IBM, Armonk, NY, USA) was used for the analyses. Continuous variables are expressed as mean ± standard deviation. Differences between the 2 groups were analyzed using the independent-samples t-test for continuous variables and $\chi 2$ test for categorical variables. Paired-samples t-test was used to compare differences of variables pre- and post-procedurally. A P value < 0.05 was statistically significant.

Results

All 38 patients were successfully performed PFO-closure guided by TEE. Procedural and intrahospital survival was 100%. Survival after a mean follow-up of 17.1 ± 1.6months was 100%.

Procedural details - PFO closure

The average time of procedure was 18.7 ± 10.5 minutes and time of mechanical ventilation was 57.3 ± 9.1 minutes. The average time of hospitalization was 2.7 ± 0.8 days and time of discharge after the operation was 1.0 ± 0.9 days. No blood transfusion was adopted in all 38 operations.

The delivery sheaths used in these operations are all 8Fr. 4 cases with atrial septal aneurysm were detected as no motion of atrial septum after the procedure. "Catheter in sheath" technique was adopted in 16 cases.

No procedural related complications occurred (valve injury, complete atrioventricular block, hematoma, hemopericardium or embolism) during follow-up. Successful PFO closure was achieved in 34 patients (89.5%). Other 4 residual shunts disappeared in the second TEE at 6 months after discharge. In the first contrast TEE at 3 months after discharge, all gradient of RLS had decreased at least 1 grade with Valsalva maneuver. Significant decrease exists in grades of RLS between pre-operation and post-operation in TEE examination. Details of PFO closure is described in Table 2.

Table 2
details of PFO closure

Variable	Value
Diameter of PFO (mm)	2.5 ± 0.8(1.5-4.0)
Occluder Selection	
18–18/25 – 18	28/10
Average operating time (minutes)	18.7 ± 10.5
Mechanical ventilation time (minutes)	57.3 ± 9.1
Hospitalization time (days)	2.7 ± 0.8
Hospitalization time after procedure (days)	1.0 ± 0.9
Immediately closed (cases)	34(89.5%)
RLS grade before operation (0°/□°/□°/□°)	0/0/12/26
RLS grade at discharge (0°/□°/□°/□°)	20/14/4/0
RLS grade at Follow-up (0°/□°/□°/□°)	36/2/0/0
Values are mean ± standard deviation.	
PFO: Patent foramen ovale; RLS: right-to-left shunt.	

Migraine with aura

After the procedure, all 28 migraines with aura alleviated at different degree. Both the migraine days and migraine attack with or without aura decreased significantly. Furthermore, the need for acute migraine medication significantly decreased after discharge($p < 0.01$). The migraine days per month decreased from 10.06 to 3.43 days($p < 0.01$) and migraine with aura days decreased from 5.72 to 2.46 days($p < 0.01$). The times of migraine attacks per day declined from 4.98 to 2.81 times($p < 0.01$) and migraine with aura attacks declined from 4.36 to 2.26 times($p < 0.01$). The need for acute migraine medication decreased from almost every day to 15.36 days($p < 0.01$) per month with downtrend every month during follow-up. MIDAS score declined significantly and BDI score significantly decreased from baseline to follow-up or discharge ($p < 0.01$). Although SF12 Physical and Mental Component scores showed no significant statistic difference before and after the procedure, the scores still show a little uptrend. 8 patients reported complete relief from migraine for at least 1 month. The average migraine days and attacks with or without aura decreased with the increasing length of follow-up. Details of migraine patients' results are shown in Table 3.

Table 3
details of migraine patients

Variable	Pre-operation (Baseline)	Post-operation (Mean in 6 months)	P Value
Migraine days per month	10.1 ± 3.3 (5.3–17.8)	3.4 ± 1.7 (0.2–6.2)	< 0.01
Migraine with aura days per month	5.7 ± 2.3 (2.1–9.2)	2.5 ± 1.3 (0.2–5.3)	< 0.01
Migraine attacks per day	5.0 ± 1.5 (3.2–8.2)	2.8 ± 1.4 (1.0-6.2)	< 0.01
Migraine with aura attack per day	4.4 ± 1.1 (2.8–6.7)	2.3 ± 0.8 (0.9–3.4)	< 0.01
Days with acute migraine medication use	29.5 ± 0.7 (27.8–30)	15.4 ± 2.9 (11.8–20.7)	< 0.01
MIDAS score	30.5 ± 4.5 (22–37)	9.2 ± 3.1 (5–12)	< 0.01
BDI score	7.8 ± 2.3 (5–12)	3.7 ± 1.5 (1–6)	< 0.01
SF12 Mental Component score	45.5 ± 3.0 (41–52)	48.4 ± 3.4 (42–54)	0.15
SF12 Physical Component score	52.5 ± 3.2 (47–58)	53.1 ± 3.0 (48–58)	0.34
Values are mean ± standard deviation.			

Cryptogenic stroke or TIA

All 10 patients suffering from pre-operational cryptogenic stroke survived and showed no evidence for recurrence of stroke (fatal or non-fatal), peripheral embolism or TIA during follow-up. 2 case with migraine was reported with freedom of migraine at the 3rd month after the procedure.

Safety and adverse events

There were no serious adverse events in the PFO closure procedure, reported by other reaserchers[15, 16], including device-related (transient atrial fibrillation, general fatigue or syncope) and related to the implant procedure (access site bleeding, retroperitoneal hematoma or another bleeding), and unrelated events. During follow-up, there was no device-related side effect.

Discussion

PFO is the most common congenital heart defect. It has been historically associated with several pathological conditions, with varying strength of evidence, most importantly with stroke but also with other diseases like platypnea-orthodeoxia, decompression illness, systemic and coronary embolization, obstructive sleep apnoea, migraine headache with aura and pulmonary embolism[17]. With a PFO large proportion in the general population, it is quite difficult to make a strong link between PFO and some specific pathological condition. Therefore, preventive PFO closure for some disease like that mentioned above is a subject of great controversy. Therefore, numerous clinical trials investigate the effect of PFO closure to prevent neurological events. Among these, three ongoing clinical trials (PRIMA[17], PREMIUM[6] and EASTFORM[18]) focus on migraine. Even though patients suffering from migraine with aura did benefit from PFO closure in the PREMIUM trial, the PFO closure is still needed more trial to prove its therapy value for migraine. Maybe the PRIMA trial, an ongoing trial, could give us the answer. In our study, we enrolled migraine with aura patients based on the PREMIUM trial selection process with a favorable outcome.

For cryptogenic stroke patients, PFO closure has been studied intensely including CLOSURE I[19], PC[20], RESPECT[21], CLOSE[22] and Gore REDUCE[23] Based on all the above 5 RCTs, we can conclude PFO-closure devices decrease the risk of recurrent stroke compared with medical therapy in patients with cryptogenic stroke[16]. Some study[24] reported stroke may re-attack after PFO-closure and 6-months antiplatelet or anticoagulation therapy. This may relate with a too big device which was difficult covered by new endocardial tissue in the 6-months regular antiplatelet therapy period. So longer antiplatelet or anticoagulation therapy may be recommended for the PFO-closure with the big device. In our study, none of the patients with cryptogenic stroke suffered from a stroke during follow-up. Although the follow-up time is not very long and the cases number is limited, our good results still can to some extent prove PFO-closure is an effective prevention for recurrent stroke after cryptogenic stroke.

In 1992, TEE had been considered as the most helpful tool of screening PFO in patients with stroke who are less than 45 years of age and in those without clinical evidence of heart disease[25]. TEE is crucial for PFO and PFO closure for years[26]. With the great application of guiding of simple congenital heart disease for transthoracic intervention in China[27, 28], TEE has been reconsidered changing its role from diagnosis to therapy guiding for structural heart disease. Even in the publication focusing on fluoroscopy for PFO closure[7, 8] TEE has been confirmed as helpful in complex anatomy. Low complication rates of PFO closure are required to justify its therapeutic role in the prevention of neurological events. Despite the device-related complications, procedure-related complications, including atrial fibrillation, hematomas, or transient hypotension[16, 29] are supposedly linked with inaccurate fluoroscopy guiding which means the wire may lead to the complication mentioned above when it tried to pass the PFO or when it be put in the left pulmonary vein to assure that it had passed the PFO. We presumed that atrial fibrillation was associated with over-stimulating when the wire in the left pulmonary vein and hematomas or transient hypotension was related to stimulation of wire by poking endocardium when it attempted to get through PFO. More centers had adopted TEE combined with fluoroscopy guiding for percutaneous PFO closure to a lower rate of total adverse events and reduce radiological exposure[30]. One of the greatest strengths of

this strategy is to allow two monitoring systems to play complementary effect for each other. In fact, from our point of view, there is no need for fluoroscopy guiding in PFO closure as our study proved. In our study, we used TEE as the only guiding tool instead of fluoroscopy guidance or mixed fluoroscopy and TEE guidance. We could achieve the same safety and efficacy with lower cost and higher resource utilization. This may be of particular importance for the area with unevenly distributed medical resources such as China. Acquiring more data will help to evaluate if PFO closure is beneficial for patients with neurological events. Our experience proved the feasibility of TEE guidance for PFO closure. After appropriate training echo guided PFO closure might prove to be as effective as fluoroscopy-guided PFO closure. Furthermore, it might be a simpler procedure with fewer complications with advantages in cost-effectiveness.

TEE provides more accurate and real-time monitoring when it guides PFO closure[31].

When applying TEE guidance, all devices including sheath, catheter or wire are monitored in real-time. Any change of angle or position of objectives could not be missed by the dedicated operator. This is why we could apply “Catheter in sheath” technique which is difficult for fluoroscopy guiding. When we apply “Catheter in sheath” technique under fluoroscopy guiding, the angle change by torquing the sheath is difficult to judge which angle is the best because fluoroscopy can only project all objectives into a flat and cannot reflect the 3-dimensional relationship of the objectives. TEE can perfectly solve this problem and provide more accurate guiding and more accuracy leads to safer procedures with fewer complications.

Limitation

This retrospective study includes an only limited number of patients providing short-term follow-up only. Randomization to standard therapy such as fluoroscopy-guided PFO closure is need. Larger patient numbers, longer follow-up time and RCT are needed in the future.

Conclusion

First clinical experiences showed that percutaneous TEE guided PFO closure is safe and effective. Both patients with migraine and cryptogenic stroke showed benefit from PFO closure.

Declarations

Ethical Approval and Consent to participate: Study approval was obtained from the Committee on Clinical Applications at the Second Xiangya Hospital and informed consent was obtained from the patients or patients’ parents (<18 years old).

Consent for publication: Publication consents have been got by all authors.

Availability of data and materials: Yes.

Competing interests: No.

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Authors' contributions:

Tianli Zhao: study designing and surgical operation;

Qin Wu: TEE guiding;

Hendrik Ruge: editing the draft;

Rüdiger Lange: technique support;

Yifeng Yang: technique support;

Zheng Jiang: provide neurological advice;

Weizhi Zhang: surgical operation;

Wancun Jin: TEE guiding;

Haisong Bu: data collection;

Shijun Hu: manuscript writing and drawing.

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References

1. Kent DM, Dahabreh IJ, Ruthazer R, Furlan AJ, Reisman M, Carroll JD, Saver JL, Smalling RW, Juni P, Mattle HP *et al*: **Device Closure of Patent Foramen Ovale After Stroke: Pooled Analysis of Completed Randomized Trials**. *J Am Coll Cardiol* 2016, **67**(8):907-917.
2. Rayhill M, Burch R: **PFO and Migraine: Is There a Role for Closure?** *Curr Neurol Neurosci Rep* 2017, **17**(3):20.
3. Lilly LS: **Pathophysiology of heart disease: a collaborative project of medical students and faculty**: Lippincott Williams & Wilkins; 2012.
4. Hara H, Virmani R, Ladich E, Mackey-Bojack S, Titus J, Reisman M, Gray W, Nakamura M, Mooney M, Poulose A *et al*: **Patent foramen ovale: current pathology, pathophysiology, and clinical status**. *Journal of the American College of Cardiology* 2005, **46**(9):1768-1776.

5. Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, Marks DS, Tirschwell DL: **Closure of patent foramen ovale versus medical therapy after cryptogenic stroke**. *The New England journal of medicine* 2013, **368**(12):1092-1100.
6. Tobis JM, Charles A, Silberstein SD, Sorensen S, Maini B, Horwitz PA, Gurley JC: **Percutaneous Closure of Patent Foramen Ovale in Patients With Migraine: The PREMIUM Trial**. *Journal of the American College of Cardiology* 2017, **70**(22):2766-2774.
7. Fateh-Moghadam S, Steeg M, Dietz R, Bocksch W: **Is routine ultrasound guidance really necessary for closure of patent foramen ovale using the Amplatzer PFO occluder?** *Catheter Cardiovasc Interv* 2009, **73**(3):361-366.
8. Mangieri A, Godino C, Montorfano M, Arioli F, Rosa I, Ajello S, Piraino D, Monello A, Pavon AG, Viani G *et al*: **PFO closure with only fluoroscopic guidance: 7 years real-world single centre experience**. *Catheter Cardiovasc Interv* 2015, **86**(1):105-112.
9. Yang Y, Zhang W, Wu Q, Gao L, Jin W, Zhao T: **Transcatheter closure of atrial septal defects without fluoroscopy: a well-established procedure for alternative use in children**. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology* 2016, **12**(5):e652-657.
10. Classification, Diagnostic Criteria for Headache Disorders CN, Cephalalgia FPJ: **Headache classification committee of the International Headache Society**. 1988, **8**(Suppl 7):1-96.
11. Johansson MC, Helgason H, Dellborg M, Eriksson P: **Sensitivity for detection of patent foramen ovale increased with increasing number of contrast injections: a descriptive study with contrast transesophageal echocardiography**. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2008, **21**(5):419-424.
12. Stewart WF, Lipton RB, Dowson AJ, Sawyer J: **Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability**. *Neurology* 2001, **56**(6 Suppl 1):S20-28.
13. Jenkinson C, Layte R, Jenkinson D, Lawrence K, Petersen S, Paice C, Stradling J: **A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies?** *Journal of public health medicine* 1997, **19**(2):179-186.
14. Beck AT, Brown GK, Steer RA, Kuyken W, Grisham J: **Psychometric properties of the Beck Self-Esteem Scales**. *Behaviour research and therapy* 2001, **39**(1):115-124.
15. Mattle HP, Evers S, Hildick-Smith D, Becker WJ, Baumgartner H, Chataway J, Gawel M, Gobel H, Heinze A, Horlick E *et al*: **Percutaneous closure of patent foramen ovale in migraine with aura, a randomized controlled trial**. *Eur Heart J* 2016, **37**(26):2029-2036.
16. Mojadidi MK, Zaman MO, Elgendy IY, Mahmoud AN, Patel NK, Agarwal N, Tobis JM, Meier B: **Cryptogenic Stroke and Patent Foramen Ovale**. *J Am Coll Cardiol* 2018, **71**(9):1035-1043.
17. Homma S, Messe SR, Rundek T, Sun YP, Franke J, Davidson K, Sievert H, Sacco RL, Di Tullio MR: **Patent foramen ovale**. *Nature reviews Disease primers* 2016, **2**:15086.

18. Xing YQ, Guo YZ, Gao YS, Guo ZN, Niu PP, Yang Y: **Effectiveness and Safety of Transcatheter Patent Foramen Ovale Closure for Migraine (EASTFORM) Trial**. *Scientific reports* 2016, **6**:39081.
19. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, Felberg R, Herrmann H, Kar S, Landzberg M *et al*: **Closure or medical therapy for cryptogenic stroke with patent foramen ovale**. *The New England journal of medicine* 2012, **366**(11):991-999.
20. Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, Andersen G, Ibrahim R, Schuler G, Walton AS *et al*: **Percutaneous closure of patent foramen ovale in cryptogenic embolism**. *The New England journal of medicine* 2013, **368**(12):1083-1091.
21. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, Tirschwell DL: **Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke**. *The New England journal of medicine* 2017, **377**(11):1022-1032.
22. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, Arquizan C, Bejot Y, Vuillier F, Detante O *et al*: **Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke**. *The New England journal of medicine* 2017, **377**(11):1011-1021.
23. Sondergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, Settergren M, Sjostrand C, Roine RO, Hildick-Smith D *et al*: **Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke**. *The New England journal of medicine* 2017, **377**(11):1033-1042.
24. Ruge H, Wildhirt SM, Libera P, Vogt M, Holper K, Lange R: **Images in cardiovascular medicine. Left atrial thrombus on atrial septal defect closure device as a source of cerebral emboli 3 years after implantation**. *Circulation* 2005, **112**(10):e130-131.
25. DeRook FA, Comess KA, Albers GW, Popp RL: **Transesophageal echocardiography in the evaluation of stroke**. *Annals of internal medicine* 1992, **117**(11):922-932.
26. Vitarelli A, Mangieri E, Capotosto L, Tanzilli G, D'Angeli I, Toni D, Azzano A, Ricci S, Placanica A, Rinaldi E *et al*: **Echocardiographic findings in simple and complex patent foramen ovale before and after transcatheter closure**. *Eur Heart J Cardiovasc Imaging* 2014, **15**(12):1377-1385.
27. Hu S, Yang Y, Wu Q, Rwakaryebe M, Liu Z, Deng Y, Wei S, Zhao T: **Results of two different approaches to closure of subaortic ventricular septal defects in children**. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2014, **46**(4):648-653.
28. Zhang F, Yang Y, Wu Q, Jin W, Bu H, Wu S, Zhao T, Hu S: **Strategy of treating secundum atrial septal defect not referred to percutaneous closure**. *Congenital heart disease* 2019, **14**(3):324-330.
29. Whisenant B, Reisman M: **PFO and Migraine**. *Journal of the American College of Cardiology* 2017, **70**(22):2775-2777.
30. Scacciatella P, Meynet I, Giorgi M, Biava LM, Matranga I, Biasco L, Omede P, Orzan F, Gaita F: **Angiography vs transesophageal echocardiography-guided patent foramen ovale closure: A propensity score matched analysis of a two-center registry**. *Echocardiography (Mount Kisco, NY)* 2018, **35**(6):834-840.

31. Bartel T, Muller S: **Contemporary echocardiographic guiding tools for device closure of interatrial communications**. *Cardiovascular diagnosis and therapy* 2013, **3**(1):38-46.

Figures

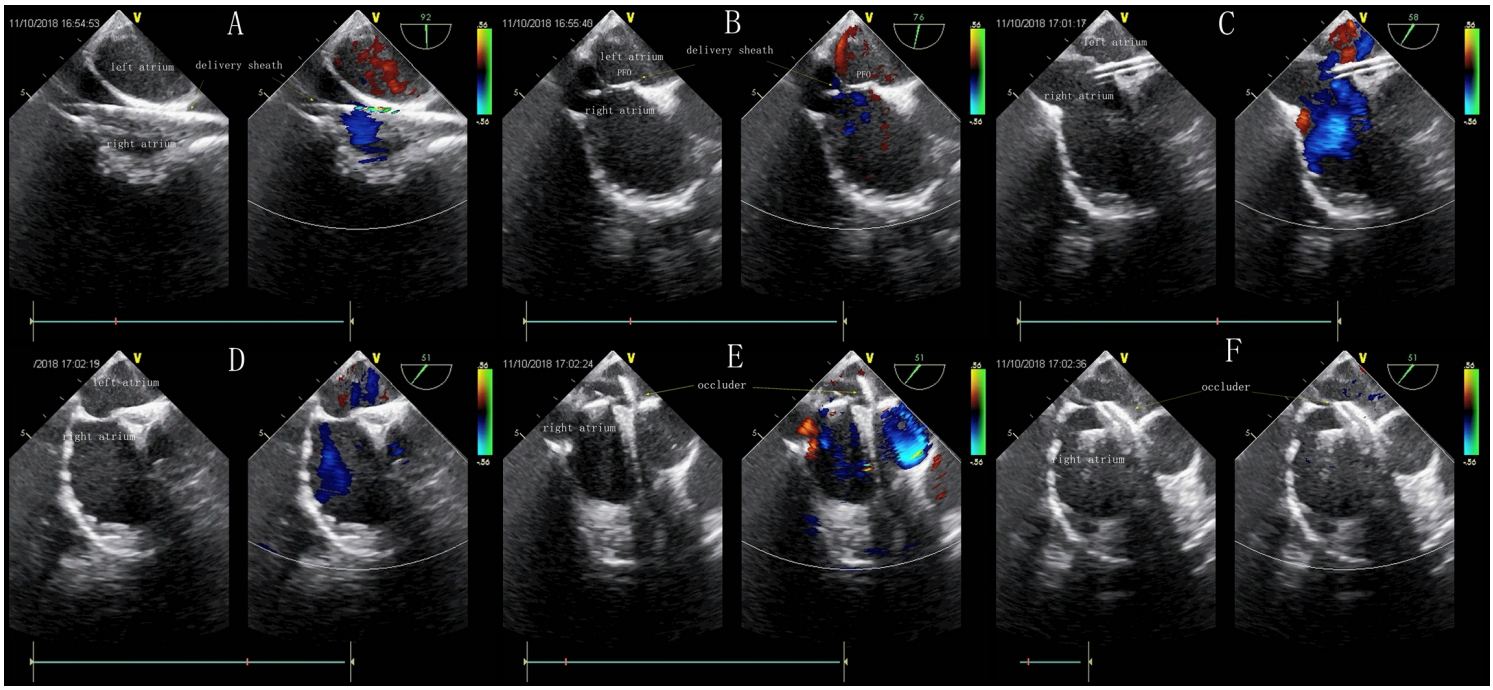

Figure 1

1A: a wire guide a delivery sheath from Inferior vena cava to superior vena cava; 1B: the loading sheath is trying to pass PFO; 1C: the delivery sheath has passed the PFO and wire is out; 1D: the PFO closure device is delivered to the left atrium; 1E: the left disc of the device is released; 1F: the right disc of the device is released and the device is fixed.

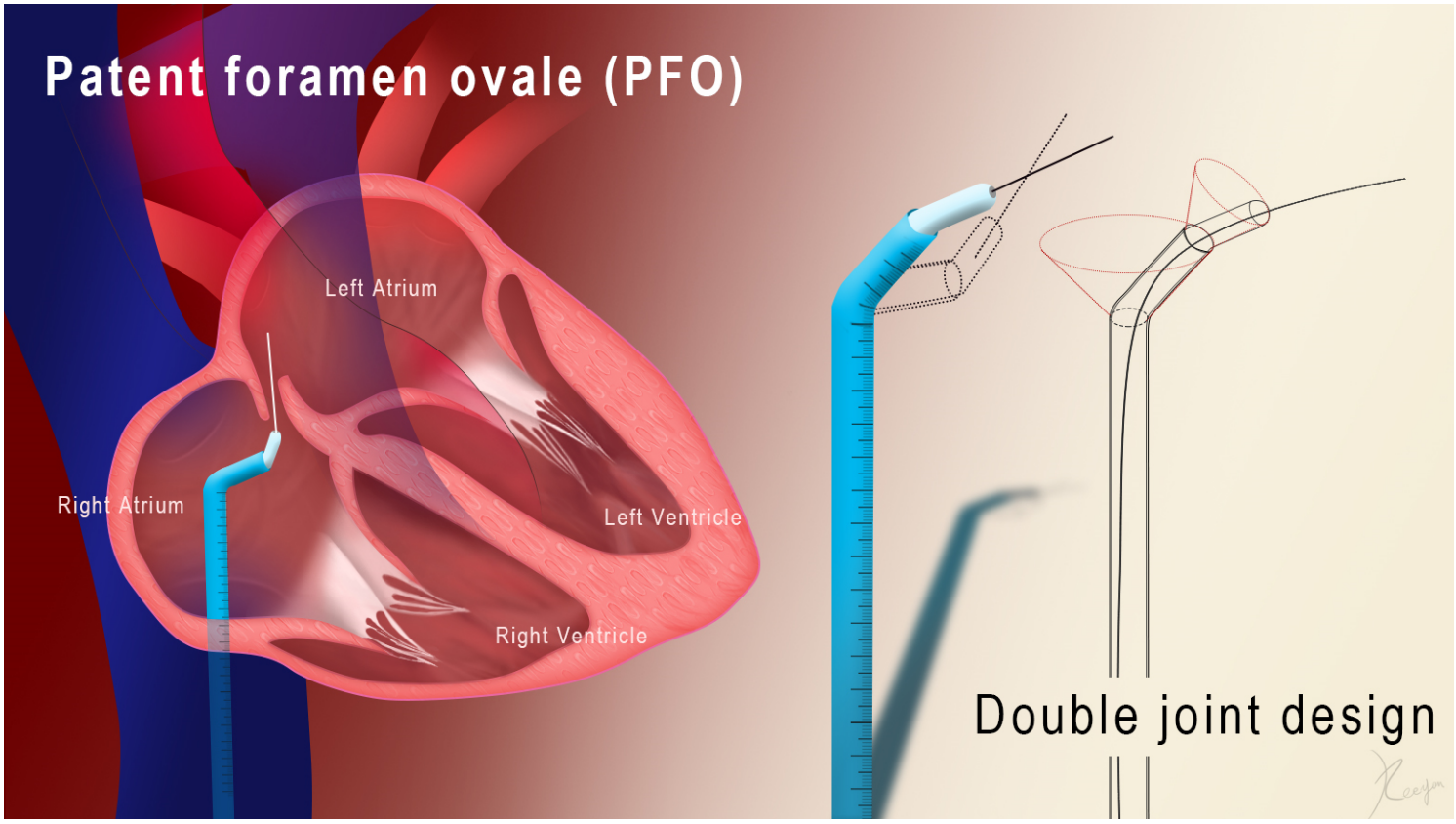

Figure 2

The schematic of "catheter in sheath" technique A 5 Fr MPA 2 diagnostic catheter is advanced in the delivery sheath, then the double joint of this combination makes the wire have multiple angles to get through PFO.