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# Multidisciplinary assessment of PFO with substantial right-to-left shunting and medium-term follow-up after PFO device closure: A single-center experience

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**Objectives:** To describe the multidisciplinary assessment of patent foramen ovale (PFO) with substantial right-to-left shunting (RLS) and medium-term follow-up after PFO closure for stroke or transient ischemic attack (TIA).

**Background:** PFO closure is a therapeutic option to prevent recurrent ischemic event in patients with cryptogenic stroke and TIA. The apparent lack of benefit seen in previous studies was in part due to the inclusion of patients with alternate mechanisms of stroke/TIA. However, the long-term follow-up results of RESPECT trial confirmed that PFO closure could reduce the recurrence rate of stroke compared to medical therapy. The obvious difference between RESPECT and the other studies is that RESPECT recruited more relevant patients with substantial RLS.

**Methods:** From May 2013 to October 2015, all subjects diagnosed as cryptogenic stroke or TIA with substantial RLS who underwent PFO closure at our institution were included. All patients underwent multidisciplinary assessment to exclude stroke/TIA with definite etiology. Baseline characteristics, clinical manifestations, procedural, and follow-up data were reviewed.

**Results:** A total of 219 consecutive patients with substantial RLS undergoing PFO closure were identified. There were no procedure-related deaths, strokes, or TIA. Mean follow-up was 2.0 ± 0.7 years. Early residual shunting was visible in 9 patients (4.1%); however, during follow-up, only 3 patients (1.4%) had residual RLS detected by contrast transthoracic echocardiography (cTTE). The annual risk of recurrent ischemic stroke or TIA was 0.457%.

**Conclusions:** PFO closure can be performed safely and effectively in patients with cryptogenic stroke or TIA. In selected patients with substantial RLS, following appropriate multidisciplinary assessment, excellent results with low incidence of recurrent events may be achieved.

**KEYWORDS**

closure, cryptogenic stroke, medium-term outcomes, patent foramen ovale, right-to-left shunting, transient ischemic attack

## 1 | INTRODUCTION

In recent years, transcatheter device closure of PFO has been used as a treatment option for the prevention of recurrent cryptogenic stroke or TIA. While PFO is noted in up to 25% of individuals,[1,2] 25% of all ischemic strokes are cryptogenic,[3] and PFO presents in 40–50% of cryptogenic stroke patients,[4,5] suggesting that the passage of a thrombus from the right to the left atrium across the PFO may be the causative mechanism.[6–8]

Although several studies have demonstrated the safety and efficacy of transcatheter PFO closure,[9] the results of a series of RCTs showed that, compared with medical treatment, PFO closure did not

show an obvious superiority.[10–12] The debate regarding which type of cryptogenic stroke or TIA requires further intervention has recently been a hot topic in the field. Significant differences between the prevention of cryptogenic stroke or TIA recurrence and medical treatment have not been observed. This may be because many patients included in the study had a PFO in conjunction with cryptogenic stroke or TIA, however, the PFO was not the primary cause of the cryptogenic stroke or TIA. Therefore, the appropriate multidisciplinary specialist pre-procedural assessment appears to be especially important. Only by screening out the true "pathological" PFO cases can the superiority of percutaneous PFO closure be determined. The long-term results of the RESPECT trial, which was presented at the TCT conference in 2016, also confirmed this point. The main difference between RESPECT and the other RCTs was that RESPECT recruited more relevant patients with substantial RLS. The long-term results of RESPECT support the hypothesis that PFO closure prevented PFO related recurrent strokes, while PFO closure could not prevent recurrent strokes from non-PFO related causes. Strictly speaking, the patients included in the CLOSURE I and PC trials had cryptogenic stroke or TIA with a PFO, but the PFO was not necessarily the cause of the cryptogenic stroke or TIA.

This study aims to describe the multidisciplinary assessment of patients with PFO and substantial RLS and to examine the procedural success and medium-term outcomes of PFO closure within the First Affiliated Hospital of Xi'an Jiaotong University from May 2013 to October 2015, with an emphasis on the role of formal neurology involvement in optimizing the procedural outcome.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

All subjects diagnosed as cryptogenic stroke or TIA with substantial RLS who underwent PFO closure between May 2013 and October 2015 were continuously included in the study.

Cryptogenic stroke and TIA were identified by established protocols and evaluated by 3 neurology specialists. Patients with a presumptive PFO related cryptogenic stroke or TIA must have undergone formal neurology review. The evaluations typically included computed tomography (CT) or magnetic resonance imaging (MRI), cerebral angiography (if necessary). Stroke was defined as a focal neurological deficit due to cerebral ischemia with a neuro-anatomically relevant infarct on imaging or by symptoms >24 hours. Patients with typical symptoms without observing MRI imaging changes were considered to have had a TIA. A PFO related cryptogenic stroke appeared as a single cortical or multiple small ischemic lesions (<15 mm) in the vertebrobasilar circulation without any visible vessel occlusion on angiography. Meanwhile, we excluded the patients with large cortico-subcortical infarction or confluent lesion (>15 mm) with additional lesions in multicirculatory territories.[13,14] An age criteria was not placed upon the diagnosis of cryptogenic stroke or TIA. It was worth noting that intrinsic small vessel disease such as lacunar infarcts tended to obviate the need for device closure.

cTTE and/or contrast enhanced transcranial Doppler (cTCD) were utilized to identify substantial RLS. If substantial RLS was identified (during normal respiration or the Valsalva maneuver), the diagnosis of PFO was performed using transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE). Especially if the PFO could not be diagnosed by TTE or if the patients had an atrial septal aneurysm (ASA) or membrane mobility >6.5 mm in TTE, they had to undergo TEE examination to confirm the diagnosis and to evaluate its anatomical characteristics.

All patients were required to undergo electrocardiogram (ECG) to exclude persistent atrial fibrillation and 24–72 hours Holter monitoring to exclude cerebral vascular accidents caused by paroxysmal atrial fibrillation. Carotid artery Doppler ultrasound, lower extremity vascular ultrasound, and history of venous thromboembolism and thrombophilia screening at the discretion of the treating team were necessary. If we could not distinguish intra- or extra-cardiac shunt, patients should undergo computer tomography pulmonary angiography (CTPA) to exclude pulmonary arteriovenous fistula (PAVF). The presence of large vessel atherosclerosis such as carotid stenosis, thrombophilia, arterial dissection, vasculitis, and cancer-related stroke were excluded to obviate the need for device closure.

### 2.2 | Echocardiography protocols and definitions

The GE-ViVid-E9 color Doppler ultrasound system (General Electric Corporation, Norfolk, VA) equipped with a 2–4 MHz transducer was used to perform TTE and a 4–7 MHz transducer was used to conduct TEE. If PFO could not be diagnosed by TTE or if the patients had an ASA or membrane mobility >6.5 mm in TTE, they had to undergo TEE examination to confirm the diagnosis and to evaluate its anatomical characteristics. For TTE and TEE, all the right atrial and interatrial septal characteristics other than PFO were recorded, including: ASA, membrane mobility >6.5 mm,[15] prominent Eustachian Valve (EV) and Chiari's network.

The severity of the shunt is a subjective assessment performed by cTTE and/or cTCD. Agitated saline was used as the contrast agent, which consisted of 8 ml of saline solution, 1 ml of air, and 1 ml of blood from the patients. Contrast agent was injected into the left cubital vein as a bolus. When using cTTE, the apical four-chamber view was generally selected. The presence of RLS was confirmed when micro bubbles (MBs) were seen in the left atrium within the first 3 cardiac cycles after contrast appearance in the right atrium during normal respiration or the Valsalva maneuver. According to Li Yue, etc.,[16] the severity of RLS was semi-quantified into a four-level scale, and we defined substantial RLS >30 MBs.

According to current standard,[17] cTCD with a TCD monitoring device (DWL MultidopX, ScanMed Medical, Gloucestershire, UK) can also be used to identify the degree of RLS. Both middle cerebral arteries were simultaneously monitored through the temporal window using 2 MHz probes. The contrast agent was used as mentioned above. This procedure was performed three times. The presence of RLS was confirmed when high-intensity transient signals (HITS) appeared within 25 seconds after contrast agent injection during normal respiration and the Valsalva maneuver. The severity

of RLS was semi-quantified into a four-level scale, and we defined substantial RLS as shower or curtain HITS.

### 2.3 | PFO closure

Antibiotic therapy was administered intravenously 1 hour before the procedure. The device size used for each procedure was determined according to the physician's preference. Two devices were used during the study period: the Amplatzer PFO Occluder (St. Jude Medical, Golden Valley, MN) and the Cardi-O-fix PFO occluder (Starway Medical Technology Inc. Beijing). The procedure was performed under local anesthesia. The device implantation was guided by fluoroscopy only. Venous access was established via the right femoral vein. Heparin was administered according to the patient's body weight (80–100IU/kg). All patients were investigated for early residual shunting and the presence of pericardial effusion using TTE within 24 hours following the procedure. After the procedure, all patients were treated with low-molecular-weight heparin at 10U/(kg · h) for 48 hours, aspirin 100 mg/day for 6 months, and clopidogrel 50–75 mg/day for 3 months following device implantation.

### 2.4 | Follow-up

All patients were followed at 1, 3, 6, and 12 months after device implantation and then yearly thereafter. Holter monitoring and TTE were performed to confirm the presence or absence of atrial fibrillation and device embolization. cTTE was followed up at 3 months after the procedure to observe residual RLS. If there was no residual RLS, cTTE examination was not required in future follow-up exams. If the RLS remained, cTTE examination was performed at follow-up exams until the RLS was no longer observed. All patients were followed after device implantation through questionnaires by phone calls or office visits with cardiovascular and neurological specialists. For patients with symptoms of palpitation and chest pain, Holter monitoring and electrocardiogram were needed at every follow-up exam. Patients with suspected recurrent stroke or TIA were assessed by 3 independent neurological specialists based on their symptoms, signs, and MRI imaging. Data were collected on patient baseline characteristics, indications, PFO characteristics (presence of ASA, membrane mobility >6.5 mm, prominent EV, and Chiari's network), and procedural characteristics (device used, device size, sheath size, total procedural and fluoroscopy time, procedural success, and complications). Follow-up was completed until October 31, 2016.

### 2.5 | Statistical analysis

Data analysis was performed using SPSS version 12.0.1. Summary statistics for normally distributed quantitative variables were expressed as the mean ± standard deviation. For non-normally distributed variables, we used median and interquartile range (IQR); categorical data were summarized by count and percentages. Differences in the means for continuous variables were compared using Student's *t*-test, and differences in proportions were tested by chi-squared analysis.

## 3 | RESULTS

### 3.1 | Patient characteristics

From May 2013 to October 2015, a total of 219 patients diagnosed with PFO related cryptogenic stroke or TIA with substantial RLS underwent PFO closure at the First Affiliated Hospital of Xi'an Jiaotong University. And we performed a retrospective analysis of these 219 patients.

The diagnosis substantial RLS in the 219 patients was made by cTTE and/or cTCD. cTTE was performed in 205 (93.6%) cases, while cTCD was performed in 164 (74.9%) cases, and both cTTE and cTCD were performed in 150 (68.5%) cases. Of note, 24–72 hours Holter monitoring was performed in all 219 patients (100%). The average age of the patients was 45.7 ± 13.5 years, 24 cases (11.0%) were older than 60 years old and 125 patients (57.1%) were male. The indication for closure was cryptogenic stroke in 125 patients (57.1%) and TIA in 94 patients (42.9%). TEE was used to confirm the diagnosis of PFO in 37 patients (16.9%) who had an ASA or a membrane mobility >6.5 mm in TTE imaging. TEE was also used in cases where the TTE imaging was non-diagnostic. ASA and membrane mobility >6.5 mm were noted in 27 patients (12.3%), Chiari's network and prominent EV were noted in 7 patients (3.2%), and PFO with a small atrial septal defect (ASD) was detected in 3 patients (1.4%) (Table 1).

### 3.2 | Procedural characteristics

The Amplatzer PFO occluder was used in 69 cases (31.5%), and the Cardi-O-fix PFO occluder was used in 150 cases (68.5%). Local anesthesia was used in all 219 cases (100%). The mean procedure time was 24.7 ± 6.8 minutes. The mean fluoroscopy time was 3.4 ± 0.9 minutes (Table 2).

Technical success was defined as the delivery and release of the device and was achieved in all 219 patients (100%). Procedural success, defined as implantation without in-hospital serious adverse events (SAEs), was also achieved in all 219 patients (100%). In four patients undergoing closure using the Cardi-O-fix PFO occluder (type 18/25) and two patients using the Amplatzer PFO occluder (type 18/25), the device prolapsed from the left atrium into the right atrium but was successfully retrieved; after which, an alternative model (type 25/35) of the Cardi-O-fix PFO occluder or the Amplatzer PFO occluder were then successfully deployed. Procedural complications included two arteriovenous fistulae, two false aneurysms, one inguinal hematoma, and two pericardial effusion managed with pericardial puncture.

### 3.3 | Follow-up

Early residual shunting was visible on the color flow Doppler in nine patients (4.1%) during TTE imaging performed the day after device implantation. Residual RLS was detected by cTTE in 3 patients (1.4%) at 180 days after the procedure; the median time to

**TABLE 1** Baseline characteristics

| Variable | PFO closure cohort (*n* = 219) |
|---|---|
| Demographics | |
| Mean age, yrs | 45.7 ± 13.5 |
| >60 years, *n* (%) | 24 (11.0) |
| Male, *n* (%) | 125 (57.1%) |
| Qualifying event | |
| Cryptogenic stroke, *n* (%) | 125 (57.1%) |
| TIA, *n* (%) | 94 (42.9%) |
| Preclosure echocardiographic findings | |
| ASA, *n* (%) | 21 (9.6%) |
| Membrane mobility >6.5 mm, *n* (%) | 6 (2.7%) |
| Chiari's network, *n* (%) | 5 (2.3%) |
| Prominent EV, *n* (%) | 2 (0.9%) |
| ASD, *n* (%) | 3 (1.4%) |
| Baseline right-to-left shunt grade | |
| Substantial shunt, *n* (%) | 219 (100%) |
| Cerebral imaging | |
| MRI, *n* (%) | 201 (91.8%) |
| CT, *n* (%) | 18 (8.2%) |
| Carotid artery imaging, *n* (%) | 185 (84.5%) |
| Holter monitor, *n* (%) | 100 (100%) |
| CTPA, *n* (%) | 28 (12.8%) |

PFO, patent foramen ovale; TIA, transient ischemic attack; ASA, atrial septal aneurysm; EV, Eustachian valve; ASD, atrial septal defect; MRI, magnetic resonance imaging; CT, computed tomography; CTPA, computer tomography pulmonary angiography.

the follow-up echocardiography was 154.5 ± 35.7 days. Patients with cryptogenic stroke or TIA were followed for a mean of 2.0 ± 0.7 years to assess for recurrent stroke, TIA, atrial fibrillation and death. One patient died during the study period because of lung cancer.

The rate of recurrent stroke or TIA in our cohort was 0.457 per 100 patient-years (Table 3). One patient, in which the Cardi-O-fix occluder (type 18/25) was used, experienced TIA recurrence 1 month after the procedure; and 1 case, in which the Amplatzer device was used, experienced TIA recurrence 3 months after the procedure. Among these two cases of TIA recurrence, 1 patient had small residual shunting. The other patient had no visible RLS detected by cTTE 180 days after the procedure, suggesting an alternative cause for the TIA. Two cases of paroxysmal atrial fibrillation (occurred at 2 weeks and 3 months after the procedure) were observed in patients in which the Cardi-O-fix PFO occluder was used; 1 reverted spontaneously to sinus rhythm and the other underwent pharmacologic conversion to sinus rhythm. One case of paroxysmal atrial fibrillation occurred in a patient in which the Amplatzer device had been used and underwent pharmacologic conversion to sinus rhythm. No cases of occluder translocation, erosion, pericardial effusion, and puncture site bleeding was found in this patient cohort.

**TABLE 2** Procedural characteristics

| Variable | PFO closure cohort (*n* = 219) |
|---|---|
| Occluder | |
| Amplatzer PFO occlude, *n* (%) | 69 (31.5%) |
| Cardi-O-fix PFO occlude, *n* (%) | 150 (68.5%) |
| Occluder type, mm | |
| 18/18 | 3 (1.4%) |
| 18/25 | 134 (61.2%) |
| 25/35 | 40 (18.3%) |
| 30/30 | 42 (19.2%) |
| Technical success, *n* (%) | 219 (100%) |
| Procedural success, *n* (%) | 219 (100%) |
| Early shunt, *n* (%) | 9 (4.1%) |
| Procedural complication, *n* (%) | 7 (3.2%) |
| Arteriovenous fistula | 2 |
| False aneurysm, | 2 |
| Hematoma | 1 |
| Pericardial effusion | 2 |
| Residual RLS, *n* (%) | 3 (1.4%) |

PFO, patent foramen ovale; RLS, right-to-left shunting.

## 4 | DISCUSSION

Although PFO combined with cryptogenic stroke or TIA was widely investigated in previous observational studies and RCTs, the relevant reports for the degree of RLS are rare, especially patients with PFO and substantial RLS. Previously, a considerable number of patients with minimal or moderate RLS have been included in studies. Sorensen described the degrees of RLS in 5 studies,[18] it was surprising to find that in the PICSS and SPARC studies, the proportion of patients with less than 10 MBs had reached 59 and 75%, respectively. In the CLOSURE I, RESPECT and PC trials, the proportion of patients with less than 25 MBs (minimal to moderate shunts) were 82, 39, and 77%, respectively. However, in the U.S. State of Utah UPSG center, Sorensen analyzed 2,700 cases of patients with PFO occlusion and found that 99% had substantial RLS. In more than 700 cases of PFO closure at the First Affiliated Hospital of Xi'an Jiaotong University, the vast majority have been diagnosed with substantial RLS. Whether this was because too many minor RLS cases were included, to a certain extent, the results of the above RCTs were not clear. Of the three RCTs, only the RESPECT trial had positive results; however, since it had included some mild to moderate RLS patients, some limitations also exist in that study. Nevertheless, the RESPECT trial identified that the patients with substantial RLS experienced the greatest benefit. Therefore, the present study was conducted to specifically investigate the recurrence risk of stroke or TIA after PFO closure by multidisciplinary assessment in patients with substantial RLS, as determined by cTCD and/or cTTE.

Similar to the previous studies,[19,20] technical success and procedural success were achieved in all 219 patients, confirming the safety of the transcatheter closure of PFO procedure. Meanwhile,

**TABLE 3** Outcomes following percutaneous PFO closure

| Outcome | Incidence per 100 patient-years |
|---|---|
| Stroke or TIA | 0.457 |
| Atrial fibrillation | 0.684 |
| Death | 0.228 |

TIA, transient ischemic attack.

annual incidence of recurrent neurological events in this study was low (0.457%), which was lower than that reported in previous RCTs.[10–12] The rate of recurrent stroke was 0.66 and 0.5% in the RESPECT and PC trials, respectively; the mean follow-up duration was 2.8 years and 4.1 in the RESPECT and PC trials, respectively. Altogether, the previous RCTs including CLOSURE I, RESPECT, and PC trials showed that the recurrence rates of stroke or TIA were higher than the rates reported in this study. The reason for this may be due to experimental design flaws and the high incidence of complications from the occluders used in the previous studies. In addition to these reasons, one of the most important reasons may be the inclusion of patients with minimal or moderate RLS in these studies. In contrast, all of the patients included in the present study had substantial RLS, which was confirmed by cTCD and/or cTTE.

In addition, the collaboration between cardiologists and neurologists was important for proper patient selection. In 2013, Italy summarized the multidisciplinary collaborations in the management of patients with PFO and cryptogenic stroke.[21] The findings above suggests that cryptogenic stroke associated with a PFO requires an in-depth diagnostic evaluation to investigate the possibility of causality between the two factors and to simultaneously stratify the likelihood of recurrence. To educate patients regarding treatment strategies, we need a local heart/brain term. Patients are advised to get involved in the decision-making process.

After the diagnosis of cryptogenic stroke (excluding atrial fibrillation, large vessel atherosclerosis, intrinsic small vessel disease, PAVF, etc.) or TIA by neurology specialists, and examination by cTCD and/or cTTE, we determined that PFO with substantial RLS highly correlated with cryptogenic stroke or TIA. Since all of our patients underwent 24–72 hours Holter monitoring, persistent, or paroxysmal atrial fibrillation can be excluded. To derive the maximum benefits from this study, careful pre-procedural assessment, including formal neurology review, aided in the exclusion of alternate etiologies.

The occurrence of recurrent stroke or TIA in our group was relatively low (0.457%). Only 2 incidents of recurrent TIA were reported. Patients who are aged 60 years old and above underwent the study procedures. Although these patients represent a highly selective group for PFO closure, the risk factors, which occurred after the procedure, were unavoidable for this particular group. Despite the safety and efficacy of the procedure, neurologic events may relapse due to other thromboembolic risk factors. Therefore, extra care should be taken in the identification of patients who would benefit from PFO closure. Among the two cases of recurrent TIA, one patient had small residual RLS. In this patient, a small ASD, which was not detected by TTE pre-procedure, was detected by TEE 180 days after the procedure. The other patient had no residual shunting detected by cTTE 180 days after procedure, therefore, suggesting an alternate cause for the TIA.

The Cardi-O-Fix PFO occluder is the only specially made closure device that has been approved by China FDA. Its characteristics are similar to the Amplatzer PFO occluder and operates in a similar manner to the Amplatzer device. The Amplatzer PFO occluder is widely used in clinical practice for percutaneous PFO closure. However, whether the clinical application of the Cardi-O-Fix PFO occluder is similar to the Amplatzer PFO occluder, remains unknown. In this study, we observed that the procedural and technical success rates of the Amplatzer PFO occluder and the Cardi-O-Fix PFO occluder were both 100%. One case using the Cardi-O-fix occluder and one case using Amplatzer device resulted in TIA recurrence after the procedure. Thus, we speculate that there was no significant difference in the efficacy and safety of the Cardi-O-fix occluder compared to the Amplatze occluder in the treatment of PFO.

Serious complications directly associated with the procedure were rare in our study group. Atrial fibrillation after the procedure was paroxysmal and all cases were resolved spontaneously or by pharmacologic conversion back to sinus rhythm. In summary, transcatheter closure of PFO appears to be safe, effective, and rarely associated with serious complications.

### 4.1 | Limitations of the study

In our study, the follow-up time was only 2.0 ± 0.7 years. Although the recurrence of embolization usually appears within this time frame, the results may be affected. Furthermore, the limitations of this study include the retrospective design of our study, small sample size, and not performing TEE in all of the patients before PFO closure.

## 5 | CONCLUSION

Although the role of PFO in the etiology of cryptogenic stroke and TIA is still controversial, a select patient group seems to benefit from PFO closure, particularly the patients with substantial RLS. In this multidisciplinary pre-procedural assessment, the transcatheter closure of PFO was found to be safe and effective. Excellent long-term results with low incidence of recurrent events may be achieved by collaborating with stroke neurologists to exclude alternate mechanisms of cerebral ischemia. Cerebral ischemia after PFO closure may reflect additional risk factors unrelated to paradoxical embolism. Although the transcatheter procedure is safe and is associated with a low rate of early complications, careful selection of candidates for PFO closure is essential.

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