Transcatheter Closure of Patent Foramen Ovale in Chinese Patients With Paradoxical Embolism
– Immediate Results and Long-Term Follow-up –

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Background: The aim of the present study was to assess immediate and long-term clinical outcome of Chinese patent foramen ovale (PFO) patients with paradoxical embolism who underwent transcatheter PFO closure.

Methods and Results: One hundred and ninety-two patients underwent transcatheter PFO closure for secondary prevention of thromboembolic events (TE). During the procedure, 7 patients had frequent atrial premature beats or transient atrial tachycardia in implantation and 1 patient had a transitory ST-elevation in leads II, III and aVf. These complications converted spontaneously after a few minutes. No cases of procedure-related death or TE were observed during hospitalization. Minor adverse events, including chest discomfort (11%), palpitations (25%) and dyspnea (1%) were reported within 1 month of the procedure. These symptoms had disappeared in most patients by 6-month follow-up. One patient had a new occurrence of migraine at 27 months after the implantation. Within a median follow-up of 49±8 months, no residual shunt of the atrial level was identified and correct positioning of the device was confirmed on transthoracic echocardiography in all patients. No death related to any cause or recurrent TE were recorded.

Conclusions: Transcatheter PFO closure is a minimally invasive procedure with a high success rate, low complication rate and an excellent long-term outcome, and appears to be a wise approach for secondary prevention of recurrent embolic events in symptomatic patients. (Circ J 2011; 75: 1867–1871)

Key Words: Follow-up; Occlusion; Paradoxical embolism; Patent foramen ovale

Patient foramen ovale (PFO) is an anatomical variant of the interatrial septum with an overall prevalence of 27% in autopsy studies. PFO has been associated with cryptogenic stroke and migraine headaches, and increasingly recognized as a source of paradoxical embolism. A high prevalence of PFO has been reported in approximately 50% of patients with cryptogenic transient ischemic attack (TIA) or ischemic stroke, suggesting an association between the presence of PFO, with or without atrial septal aneurysm (ASA), and thromboembolic events (TE). The optimal management for the prevention of a paradoxical embolic event in these patients remains controversial. Medical therapies with anticoagulants or antiplatelet agents, surgical PFO closure and percutaneous transcatheter closure of the PFO have been proposed as therapeutic options.

The results of several randomized clinical trials, randomized controlled trials and reports of single-center experience have indicated that transcatheter PFO closure is a potential option for patients with PFO and thromboembolic phenomena, in that it avoids the morbidity associated with surgical closure or lifelong anticoagulation therapy. Despite the good short-term results of transcatheter PFO closure in these patients, however, the long-term data are limited, especially in Chinese patients. The aim of the present study was therefore to assess the long-term clinical outcome in PFO patients with paradoxical embolism who underwent transcatheter PFO closure in a single center.

Methods

Patients
Between January 2005 and May 2010, 192 patients who were referred for transcatheter closure of a PFO following 1 or more presumed paradoxical systemic events were included in the present study. A TE was considered to be due to a paradoxical embolism when the following criteria were met: presence of PFO with spontaneous or provokable right-to-left shunt during transthoracic echocardiography (TTE)/trans-
esophageal echocardiography (TEE); clinical and/or radiologic evidence (computed tomography [CT], magnetic resonance imaging [MRI], or angiography) of an ischemic stroke, a TIA (defined as a focal neurologic deficit resolving completely within 24 h), or an extracranial peripheral thromboembolic episode. Exclusion criteria were active infection at the time the transcatheter procedure was scheduled; pregnancy; thrombus at or near the PFO on TTE/TEE; coagulation disorders; presence of an atrial septal defect; and a history of stroke or TIA within the past 14 days. All patients underwent thorough and rigorous evaluation to exclude any other causes of systemic embolism. Patient evaluation depended upon the case and included neurological examination, brain CT or MRI, extracranial Doppler ultrasonography, 12-lead electrocardiogram (ECG), 24-h blood pressure and ECG monitoring, 2-D echocardiography with microbubble test with and without the Valsalva maneuver, TEE, and Doppler of lower extremities to exclude deep vein thrombosis. The study protocol was approved by the Institution’s Ethics Committee and informed consent was obtained from every patient.

Echocardiography Definitions
The ultrasound machine used was Vivid-7 (GE Medical Systems, USA). All echocardiography was done with a multiplane TEE probe, using 10 ml of agitated saline solution as the contrast agent. PFO was defined as a flap-like opening in the atrial septum secundum, with the septum primum serving as a 1-way valve allowing for permanent or transient right-to-left shunt. ASA was defined as the presence of a localized protrusion of the fossa ovalis, with a base width ≥15 mm and mobile septum excursion ≥10 mm into the left or right atrium. The PFO size was additionally determined by multiplane 2-D TEE as recently reported by Schuchlenz et al.12 Spontaneous or provoked right-to-left shunt was semi-quantitatively graded according to the number of bubbles detected in the left atrium after crossing the interatrial septum on a still frame: grade 0, none; grade 1, minimal (1–5 bubbles); grade 2, moderate (6–20 bubbles); and grade 3, severe (>20 bubbles).

Implantation Procedure
The implantation technique has been described in detail elsewhere.13 The procedure was carried out under TTE guidance. The Spider™ PFO Occluder and Amplatzer PFO occlusion system were used according to availability. The description of these devices has been provided previously.13,14 The Spider™ PFO Occluder (Lifetech Scientific (Shenzhen), China; Figure) is a self-expandable, double disk device and is composed of a right disk composed of ceramic-coated nitinol wire mesh and a left disk composed of expanded polytetrafluoroethylene membrane with 4 or 6 ceramic-coated braided nitinol anchors, which may minimize the risk of thrombus formation and increase the speed of complete endothelialization. The joint between the left and right disks allows them free rotation. The design of the occluder allows it to adapt to the unique morphology of a PFO.

For prophylaxis of TE after device implantation, all patients were treated with aspirin at 100 mg once daily for 6 months, except in patients with contraindications.

Follow-up
TEE, chest X-ray and routine ECG were performed at 24 h after transcatheter PFO closure. Clinical and echocardiographic follow-up was performed at 1 month, 3 months, 6 months, and 12 months after occlusion, then yearly thereafter. Follow-up included extensive neurological (by a neurologist experienced in cerebrovascular diseases) and medical examination, and standard ECG, and echocardiography at rest and during Valsalva maneuver. Residual shunt of the atrial level follow-up was reviewed and assessed on 2-D and color flow Doppler echocardiography. Follow-up events included death, recurrent neurological or peripheral TE, and the need for re-intervention for significant residual shunt or device malalignment. Patients with suspected recurrent TE were re-evaluated on cerebral CT and/or MRI. Twenty-four-hour Holter monitoring was performed in the majority of patients within 6 months after PFO closure.

Statistical Analysis
Continuous variables are expressed mean±SD. All statisti-
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Results

Patient Characteristics

Between January 2005 and May 2010, 192 patients with a PFO and ≥1 TE underwent percutaneous PFO closure. Patient characteristics are summarized in Table. There were 115 women (60%) and 77 men (40%) with a mean age of 34±14 years. Indications for PFO closure included ischemic stroke in 58 patients, TIA in 65 patients, other peripheral embolisms in 7 patients, a repeated migraine history in 65 patients, and decompression sickness in 1 underwater diver. Ninety-two patients also had platypnea/orthodeoxia syndrome. Twenty-five patients (13%) had a history of more than 1 TE prior to PFO closure, and an ASA was present in 53 patients (28%). Cardiovascular risk factors were identified as hypertension in 43 patients (22%), diabetes mellitus in 7 patients (4%), smoking in 58 patients (30%) and hyperlipidemia in 16 patients (8%).

Procedural Outcomes

The PFO occluder was implanted successfully in all patients. The PFO diameter assessed on TEE was 12±3 mm. Of the 192 patients who underwent percutaneous PFO closure, the Amplatzer device was used in 137 (71%) and the Spider PFO Occluder in 55 (29%). The size of the Amplatzer device used was 18 mm (n=67), 25 mm (n=26), and 35 mm (n=44). The size of the Spider device used was 16 mm (n=17), 18 mm (n=9), 22 mm (n=16), 24 mm (n=8), and 26 mm (n=5). Transseptal puncture was required in 1 patient in the Amplatzer group and in 4 patients in the Spider group because of difficulty in passing the guidewire through the PFO. Full occlusion with no significant residual shunt was achieved in all patients immediately after device deployment. Total procedure time, including additional coronary angiography in 9 patients, was 47±25 min. Total fluoroscopy time was 19±7 min. During the procedure, 7 patients had frequent atrial premature beats or transient atrial tachycardia in implantation, which converted spontaneously to a normal sinus rhythm after device deployment, and 1 patient had a transitory ST elevation in leads II, III and aVf, caused by air embolism in the right coronary artery, which resolved spontaneously after a few minutes. No large echocardiographic shunt was observed in any of the patients at 24 h after the procedure. No death, cerebral embolic events, cardiac tamponade, occluder dislodgement or retroperitoneal hematoma were observed during hospitalization. TEE 24 h after implantation showed that the position and shape of the occluders were optimal, and no residual shunt was found.

Follow-up

All patients who underwent percutaneous PFO closure had completed clinical follow-ups for at least 6 months (mean, 49±8 months; range, 6–70 months). Minor adverse events, including chest discomfort (11%), palpitations (25%) and dyspnea (1%) were reported within 1 month of the procedure. These symptoms disappeared in most patients by 6-month follow-up. One patient reported a new occurrence of migraine at 27 months after the implantation of the PFO occluder, whose diagnosis of hypophysoma was confirmed on MRL. No death, related to the procedure or to any other cause, was recorded. None of the patients had recurrent stroke or recurrent TIA. No residual shunt of the atrial level was identified and a correct position of the device was confirmed on TTE in all patients. All ECGs showed sinus rhythm and a normal PQ interval. No significant abnormal homocytology blood results, renal function or liver function were found.

Discussion

PFO has been identified as a potential source of paradoxical embolism. Frequent forms of presentation of paradoxical embolism include cryptogenic stroke, peripheral embolism and decompression sickness in underwater divers. Although it is not clear how PFO causes this, it is thought to involve the passage of emboli from the right- to the left-sided cardiac chambers through the PFO. For prevention of a paradoxical embolic event, transcatheter closure of the PFO has been shown to be feasible in patients with presumed paradoxical embolism. The present investigation demonstrates that transcatheter closure of PFO is a safe and effective technique for Chinese patients with paradoxical embolism. There were no recurrent paradoxical embolic events during follow-up. There were no device-related complications. No patients required surgical removal of the device or re-intervention due to significant residual shunt, device malalignment or device-adherent thrombus formation at the left atrial disc surface.

The association between PFO and cryptogenic stroke has been described in observational clinical trials, but appropriate therapy for these patients is still undetermined. The rate of recurrent TIA and stroke in patients with cryptogenic stroke is estimated at 3.8–5.5% per year despite adequate anticoagulation or antiplatelet therapy. In a 42-center study by Homma et al, 630 stroke patients were enrolled in the Warfarin–Aspirin Recurrent Stroke Study, of whom 312 (49.5%) were randomized to warfarin and 318 (50.5%) to aspirin. PFO was present in 203 patients (33.8%). End-points were recurrent ischemic stroke or death. There was no significant difference between those with no, small, or large PFO (small PFO, P=0.41; large PFO, P=0.16; 2-year event rates for no, small, and large PFO, 15.4%, 18.5%, and 9.5%, respectively).
needed.

evaluate this strategy, randomized and multicenter trials are necessary. Therefore, to further evaluate this strategy, randomized and multicenter trials are needed.

Recently, a non-randomized, prospective, patient preference case series comparing antiplatelet therapy (44 patients) and percutaneous closure (48 patients) was published. All patients had at least 2 years of follow-up. The recurrence rates of embolic events in the medical therapy group and percutaneous closure group were 14.75% and 0%, respectively (P<0.001). In the PFO group, all patients had complete closure at 6 months and had no complications. In contrast, 6% and 13% of patients in the antiplatelet group had major and minor hemorrhagic events, respectively. Consequently, with regard to medical therapy, the presence of PFO in stroke patients may not increase the chance of adverse events regardless of PFO size or the presence of ASA. Some data also suggest that specific PFO parameters, such as the degree of right-to-left shunting, the presence of ASA, and PFO tunnel length, may increase the risk for TE and may represent the cohort of patients who will receive the greatest benefit from device closure.

The first case series reporting the successful transcatheter closure of PFO in 36 patients with presumed paradoxical events was published in 1992. Subsequently, transcatheter implantation of PFO closure devices has been reported as safe and effective, with a high success rate, low incidence of periprocedural complications, and excellent results during long-term follow-up. Although some investigators have reported a higher incidence of recurrent TE in the presence of a residual shunt (relative risk, 4.2; 95%CI: 1.1–17.8), we and others have not confirmed this finding.

The presence of an ASA has been identified by some investigators as an important factor associated with increased risk of neurological events. A 4.4% per year rate of recurrent events was reported by Mas et al in patients with both PFO and ASA treated with aspirin or oral anticoagulants. After PFO device closure, the presence of ASA is not associated with an increased incidence of recurrent embolic events. The present finding is in agreement with those of Windecker et al and supports the results of Mas et al (ie, that in the absence of a PFO, the presence of ASA alone is not associated with an increased incidence of recurrent embolic events). Thus, patients with the coexistence of ASA and PFO obtain a special benefit from percutaneous closure of the PFO, which might be explained by stabilization of the aneurysmatic atrial septum between the disks of the device and closure of the larger PFO opening associated with an ASA. The present study has demonstrated that at long-term follow-up, the incidence of recurrent embolic events is very low. Windecker et al showed that the greater number of recurrences occur within the first year after device implantation. Thus, it is possible that a more intensive antiplatelet regimen and/or warfarin anticoagulation may be necessary during the first year after device placement before there is complete re-endothelialization of the device. This approach is particularly important in patients with hypercoagulable states. The efficacy of PFO closure to prevent recurrent systemic TE has been confirmed by several clinical trials, but it has not been established using well-designed randomized control trials. Therefore, to further evaluate this strategy, randomized and multicenter trials are needed.

The low incidence of TE recurrence in the present subjects can be explained by 2 factors, namely (1) puncture technique; and (2) device type. In cases of long PFO tunnel or difficulty in passing the guidewire through the PFO, the puncture technique (utilization of a trans-septal puncture) is used to achieve better apposition of the septum primum to the septum secundum, and to avoid device deformity. The present patients underwent PFO closure with Spider and Amplatzer closure systems. These 2 closure systems are reported to be the safest and most efficacious devices in terms of periprocedural complications, incidence of recurrence of neurological TE, residual shunt at follow-up and rate of thrombus formation, thus underlining the importance of device design for successful percutaneous PFO closure.

If the PFO diameter is <10 mm, a relatively small device (Amplatzer device 18 mm, Spider device 16 mm) can be selected. If the PFO diameter exceeds 20 mm or trans-septal puncture is required, a relative larger device (Amplatzer device 35 mm, Spider device 24 or 26 mm) will be needed.

Despite the growing recognition of the PFO, particularly when associated with an ASA, as a risk factor for several disease manifestations (above all paradoxical embolism), the optimal treatment strategy remains controversial. Percutaneous transcatheter closure of PFO is a minimally invasive procedure with high success rate, low complication rate and an excellent long-term outcome. For secondary prevention of recurrent embolic events, percutaneous transcatheter closure of PFO appears to be a wise approach for symptomatic patients.

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