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Long-term outcome of transcatheter patent foramen ovale closure in patients with paradoxical embolism

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Abstract

Background: Optimal management of patients with PFO and paradoxical embolic events is still debated. Moreover, data from long-term studies on large patient populations are lacking. Aim of the study is to assess immediate and long-term clinical outcome of patients with PFO and paradoxical thrombo-embolic events submitted to transcatheter PFO closure.
Methods: Only patients with PFO-related transient ischemic attack or stroke underwent PFO closure. Patients were evaluated clinically and echocardiographically at 1, 6 and 12 months after the procedure and yearly thereafter. Primary endpoints were death, recurrent stroke or TIA. Residual right-to left shunt (RLS) was monitored by transthoracic echocardiography (TTE) or transcranial Doppler (TCD) at 6 months'follow-up.
Results: 202 consecutive patients underwent percutaneous PFO closure for secondary prevention of TE. Device migration was observed in one patient 24 h after the procedure. No cases of procedure-related death or stroke occurred during a median follow-up of 3 ± 1.3 years. Three recurrent TIAs were observed within the first 6 months of follow-up. The cumulative estimated probability of recurrent TE-free survival rate after PFO closure was 99% in patients ≤ 55 years, 84% in patients > 55 years ($p < 0.05$) and 94% and 100% in patients with PFO, with or without atrial septal aneurysm (ASA), respectively ($p < 0.05$). Of the 188 (93%) patients submitted to TTE or TCD at 6 months' follow-up, 8 (4%) presented a small RLS.
Conclusion: Transcatheter PFO closure is associated with low incidence of in-hospital complications and low frequency of recurrent TE at long-term follow-up.

Keywords: Patent Foramen Ovale; Congenital heart disease in adults; Intracardiac Echo

1. Introduction

A high prevalence of a patent foramen ovale (PFO) has been reported in approximately 50% of patients with cryptogenic transient ischemic attack (TIA) or ischemic stroke [1], suggesting an association between the presence of PFO, with or without atrial septal aneurysm (ASA), and thrombo-embolic events (TE) [2]. Optimal management of these patients remains controversial. Two randomized clinical trials are currently underway, focusing on the prevention of recurrent TE, and comparing percutaneous closure of PFO with anticoagulation or antiplatelet therapy. Moreover, four randomized controlled trials will evaluate the effectiveness of transcatheter PFO closure in the management of migraine headache. Over the last 10 years, several reports, based upon single center experience, have appeared in the international literature concerning the use of percutaneous occluder devices for PFO closure in patients with TE, in the attempt to avoid the morbidity associated with surgical closure or lifelong anticoagulation therapy [3–10]. Despite the growing interest in interventional PFO closure, data from

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long-term studies on large patient populations are still lacking. Aim of the present study was to evaluate long-term clinical outcome in a consecutive series of patients with TE who underwent percutaneous transcatheter PFO closure in a single center.

2. Materials and methods

2.1. Patients

Between January 2001 and September 2007, 202 consecutive patients with ≥1 paradoxical embolic event were referred to our Department for percutaneous transcatheter PFO closure and observed prospectively at follow-up. The study protocol was approved by the local Ethics Committee and all patients gave written informed consent to the investigation. Diagnosis of ischemic stroke was based on the signs and symptoms of a sudden neurological deficit, documented clinically by a neurologist and radiographically by either cranial computed tomography (CT) or magnetic resonance imaging (MRI). TIA was defined as a focal neurologic deficit resolving completely within 24 h. The cerebrovascular event was considered the result of a paradoxical embolism when the presence of the PFO, with or without ASA and spontaneous or provoked right-to-left shunt (RLS), was identified by trans-esophageal contrast echocardiography (TEE) in association with clinically and/or radiographically confirmed ischemic stroke or TIA and with no other identifiable cardiac, aortic or cerebrovascular disorder. All patients underwent a 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 hr blood pressure and ECG monitoring, 2D echocardiography with microbubble test with and without the Valsalva maneuver, TEE, Doppler of lower extremities to exclude deep vein thrombosis, with special attention being focused on hypercoagulable workups (proteins C and S, antithrombin III, anticardiolipin antibodies, homocysteine, factor V Leiden and lupus anticoagulant).

2.2. Echocardiographic definitions

All echocardiographic evaluations were made with a multi-plane TEE probe, using 10 ml of agitated saline solution as contrast agent. PFO was defined as a flap-like opening in the atrial *septum secundum*, with the *septum primum* serving as a one-way valve allowing for permanent or transient right-to-left shunt. Atrial septal aneurysm 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 [11]. Quantification of PFO shunt volume, as determined by contrast injection at rest and during Valsalva maneuver, was defined. A "small" shunt volume was defined as 3–20 bubbles and a "large" shunt volume as >20 bubbles passing the PFO into the left atrium.

2.3. Implantation procedure

Transcatheter PFO closure has been described in detail elsewhere [12,13].The procedure was carried out under intracardiac echocardiography (ICE) (Acunav Diagnostic Ultrasound Catheter, California, USA), TEE and transthoracic (TTE) guidance. Three different types of device were used according to the availability, at different time points, including the Amplatzer PFO Occluder (APO), Helex PFO Occluder (HPO) and Premere PFO occlusion system (PPO). On the day of implantation, 250 mg of intravenous acetylsalicylic acid and intravenous amoxicillin were administered. Three doses of amoxicillin were administered, 2 days after the procedure, for prophylaxis of bacterial endocarditis. Following sheath placement in the right femoral vein, heparinization was performed with 100 units of unfractionated heparin/kilogram of body weight. The position of the device was confirmed by chest X-ray and TTE before discharge. For prophylaxis of TE after device implantation, patients were treated with acetylsalicylic acid (300 mg) for 6 months. Standard bacterial endocarditic prophylaxis was recommended for 12 months.

2.4. Follow-up

Patients were observed at follow-up clinically and echocardiographically with TTE at 1, 6 and 12 months after the procedure and yearly thereafter. Moreover, chest X-ray, for the detection of device fracture, as well as TTE or transcranial Doppler (ce-TCD) with intravenous contrast injection, for detection of residual shunting at rest and after Valsalva maneuver, were performed at 6 months' follow-up. Residual shunting was graded following the definition used for evaluation of the PFO prior to closure, as described above All patients and family physicians were instructed to inform us of any change in clinical status. Death due to cerebrovascular embolism, stroke or TIA were considered recurrent TE and defined according to the previously stated inclusion criteria. Patients with suspected recurrent cerebrovascular TE were re-examined by a neurologist and a brain imaging study was performed. Follow-up data included also the need of reintervention for significant residual shunt or device malalignment.

3. Statistical analysis

Descriptive statistics were calculated for demographic and echocardiographic characteristics, the duration of follow-up and recurrent TE. Comparison between patients aged ≤55 and >55 years old and between patients with PFO with or without ASA were made using sample Student's tests/Wilcoxon signed rank test. Kaplan–Meier survival analysis was used to assess the probability of recurrent