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Cross-sectional observational study of patients submitted to percutaneous occlusion of patent foramen ovale: a 20-year retrospective analysis

Estudo observacional transversal de pacientes submetidos à oclusão percutânea de forame oval patente: uma avaliação retrospectiva de 20 anos

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ABSTRACT – Background: Left-to-right shunting via the foramen ovale is a potential cause of paradoxical embolism. The presence of patent foramen ovale in more than 40% of patients with idiopathic ischemic stroke has led to deeper investigation of the impact of its closure on decreasing stroke recurrence rates. This study describes 20 years of experience with percutaneous patent foramen ovale occlusion performed by a single operator. **Methods:** This sample comprised 527 patients with ischemic stroke submitted to percutaneous occlusion of patent foramen ovale associated to left-to-right shunting. **Results:** The procedure was successful in all cases. The mean age was 48 years (range of 9 to 72 years), and 57% were male. Amplatzer® and Occlutech® prostheses were implanted in 295 and 232 patients (56% and 44%, respectively). There were no deaths, and complications were as follows: hematoma at the puncture site (three patients, 0.6%), femoral arteriovenous fistula with spontaneous resolution (two patients, 0.4%), cardiac tamponade resolved after puncture and drainage (two patients, 0.4%), transient supraventricular arrhythmia (22 patients, 4.2%), headache (27 patients, 5.1%), atrial fibrillation (two patients, 0.4%), large residual shunt requiring a second prosthesis (two patients, 0.4%), recurrence of ischemic stroke within 5 years (four patients, 0.8%) and hypersensitivity to nickel (one patient, 0.2%). **Conclusion:** In this series, patent foramen ovale occlusion was a safe and effective alternative for prevention of recurrent ischemic stroke. Recurrence rates over the course of 5 years were low.

Keywords: Foramen ovale; Ischemic stroke; Cardiac tamponade; Atrial fibrillation

RESUMO – Introdução: A possibilidade de *shunt* da direita para esquerda pelo forame oval é causa potencial de embolia paradoxal. A presença de forame oval entre os pacientes com acidente vascular cerebral isquêmico criptogênico em mais de 40% dos casos despertou interesse em avaliar o impacto de seu fechamento na redução de recidiva da doença. O estudo objetiva relatar a experiência de 20 anos com fechamento percutâneo de forame oval realizado por um único operador. **Métodos:** Foram submetidos a fechamento percutâneo de forame oval associado a *shunt* da direita para esquerda 527 pacientes com acidente vascular cerebral isquêmico. **Resultados:** O procedimento foi realizado com sucesso em todos os pacientes. A média da idade foi de 48 anos (9 a 72 anos), sendo 57% do sexo masculino. Foram implantadas prótese Amplatzer® em 295 pacientes (56%) e Occlutech® em 232 (44%). Não houve mortalidade, e ocorreram as seguintes complicações: hematoma no local da punção em três pacientes (0,6%); fístula arteriovenosa femoral em dois (0,4%) com resolução espontânea; tamponamento cardíaco em dois (0,4%) com resolução após punção e drenagem; arritmia supraventricular transitória em três (0,6%); cefaleia em 27 (5,1%); fibrilação atrial em dois (0,4%); *shunt* residual grande com necessidade de segunda prótese em dois pacientes (0,4%); recorrência de acidente vascular cerebral isquêmico em seguimento em 5 anos em quatro (0,8%) e hipersensibilidade ao níquel em uma paciente (0,2%). **Conclusão**: A oclusão de forame oval como prevenção de recorrência de acidente vascular cerebral isquêmico nessa série se mostrou segura, eficaz e com baixo índice de recidiva em 5 anos de seguimento.

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INTRODUCTION

Patent foramen ovale (PFO) is an embryological remnant defined as incomplete fusion of *septum primum* and *septum secundum*, which is found in 20% to 25% of the population.[1] Although uncommon, right-to-left shunting may occur and is a potential cause of paradoxical embolism. Idiopathic ischemic stroke is the most widely investigated form of paradoxical embolism. The presence of PFO decreases with age, from 34% in the first decades of life to 20% after 80 years.[2]

More than 50% of patients with ischemic stroke may have PFO.[3] Interatrial septal aneurysm (IASA) and exuberant Eustachian valve or Chiari´s networks increase the risk of thrombus-in-transit through a PFO, and are more common in patients with PFO and ischemic stroke.[4-8] Other conditions, such as decompression sickness in divers, arterial deoxygenation syndrome, migraine and other specific high-risk clinical scenarios,[8] such as long-lasting neurosurgeries in the sitting position,[9] may be associated with or aggravated by PFO.

Systemic embolism may occur at other sites. However, the role of PFO in patients with ischemic stroke, has drawn greater attention. Paradoxical embolism through a PFO was first described by Connhein, in 1877.[10] Improvements in intracardiac shunt detection methods and the advent of safer and more user-friendly materials for percutaneous PFO occlusion have led to deeper investigation of the contribution of PFO and the value of percutaneous PFO occlusion as a secondary ischemic stroke prevention measure in the last decades.

This study consists of a series of patients submitted to percutaneous PFO occlusion in the state of Minas Gerais. Patients were treated on by the same operator over a 20-year period.

METHODS

Patients

A cross-sectional, observational descriptive study of cases seen from January 2000 to December 2020. A total of 527 patients with ischemic stroke and confirmed diagnosis of PFO, with large right-to-left shunt (spontaneous or induced by Valsalva maneuver) and eligible for percutaneous occlusion were included. Eligibility criteria were as follows: absence of lacunar stroke, carotid artery obstruction of 50% or less, sinus rhythm (24-hour Holter monitoring and event monitoring for at least 1 week) in patients aged over 60 years, absence of myocardial disease, aortic disease or left valve lesions that might explain thrombus formation, lack of hematologic contraindications for surgery in consensus with the hematology team, ischemia, PFO and right-to-left shunt detected by magnetic resonance imaging (MRI) or computed tomography (CT), spontaneous or induced by Valsalva maneuver, confirmed by echocardiography bubble study and transcranial Doppler (TCD). Patients with transient ischemia were not included. Interatrial septal aneurysm was defined as bilateral interatrial septum motion greater than 10mm.[11] In patients referred for PFO occlusion, diagnosis had been confirmed by assistant physicians using imaging methods, mostly transesophageal echocardiography (TEE). In cases of doubtful shunt quantification due TEE-related sedation or other reasons, transthoracic echocardiography (TTE) and TCD assessment of the middle cerebral artery (MCA) or the ophtalmic artery (OA) were used, whenever required. Shunts were investigated prior to and after the Valsalva maneuver. Arterial flow spectral curve analysis was based on the number of spikes and timing.

This article was analyzed and approved by the Research Ethics Committee (CAAE: 56816222.0.0000.5533).

Procedure technique

Patients were referred to the catheterization laboratory and a venous access was obtained. Prophylactic antimicrobial therapy was then started, according to the hospital protocol. With patients under light sedation, the femoral vein was punctured at one or two sites (cases requiring intracardiac echocardiography - ICE). In some particular cases, the internal jugular or one hepatic vein was punctured. The following procedures were then carried out: intravenous (IV) heparin infusion (100U/kg, up to 5.000U) following insertion of the TEE probe or the second venipuncture (cases submitted to ICE), exclusion of an intracardiac thrombus, measurement of cardiac and pulmonary cavity pressure, catheter passage to the left superior pulmonary vein through the PFO, catheter replacement with a long sheath ensuring the sheath remained in the left atrium and de-aired (detection of free-flowing blood return) and introduction of the prosthesis mounted onto the long sheath whilst keeping the sheath de-aired and free of thrombi. The left disk was then released, pulled back towards the septum and deployed at the neck under fluoroscopic and echocardiographic guidance. This was followed by right disk landing. Finally, appropriate positioning was confirmed and the prosthesis delivered (Figure 1).

In cases with large IASA or leaflet opening larger than 5mm, a balloon catheter was used to determine dilated opening size and guide prosthesis selection - PFO or atrial septal defect (ASD). Whenever balloon waist diameter was larger than 8mm, ASD prosthesis was selected.

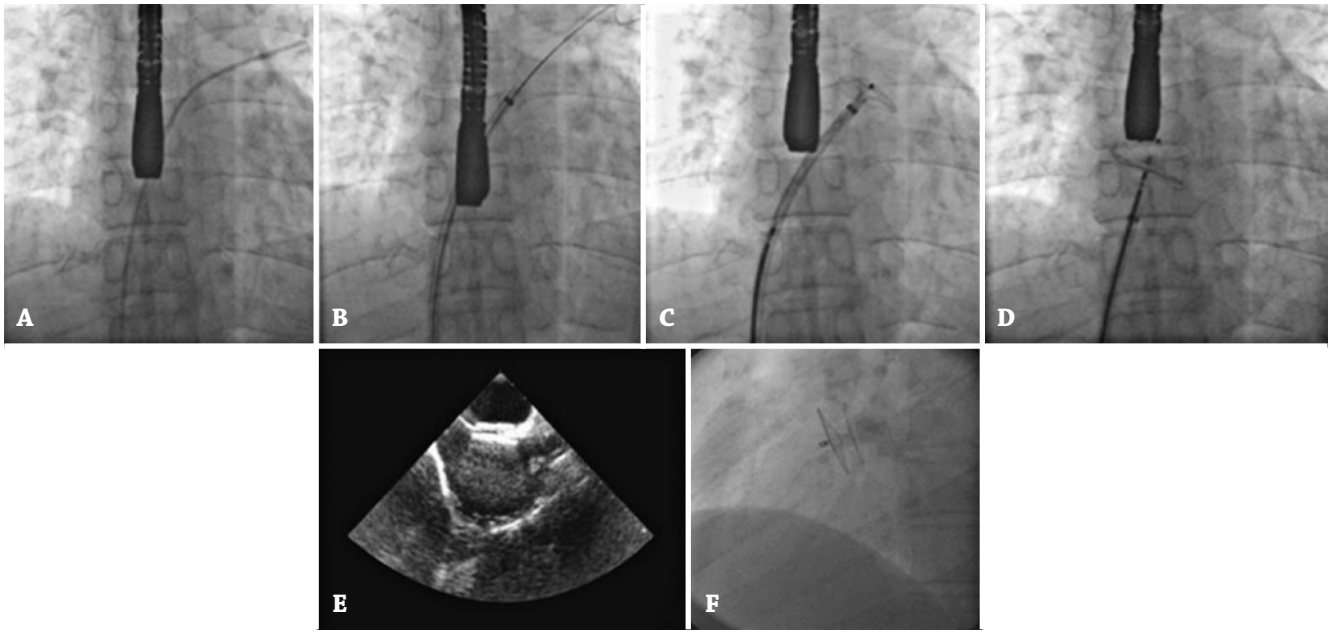

Figure 1. Left-to-right patent foramen ovale occlusion procedure stages: catheter in the pulmonary vein (A), sheath in the left atrium (B), left (C) and right (D) disk deployment, echocardiographic (E) and fluoroscopic (F) view of the prosthesis.

Post-procedure orientations

Eating and walking around the room were allowed within 1 to 2 and 4 hours after surgery, respectively. Patients were discharged from hospital within 24 hours and allowed to resume professional activities within 3 to 15 days, depending on the type of activity. Acetylsalicylic acid (ASA) was prescribed for 12 months, as follows: 200mg/day in the first 6 months, followed by 100mg/day for the next 6 months) to patients with no residual shunt. Patients aged over 50 years or with other risk factors were prescribed ASA for life. Patients allergic to ASA were treated with clopidogrel (75mg). Follow-up visits were scheduled at 1, 6, 12, 24, 36, 48 and 60 months. Patients were submitted to TTE within one month, and to TTE plus TCD after 6 months. In cases with residual shunt, diagnostic tests were repeated one year later. Patients with persistent shunt who met indication criteria were referred for occlusion.

Patients with atrial fibrillation (AF) were converted to sinus rhythm, maintained using amiodarone (200 to 400mg/day) and submitted to Holter monitoring within 2, 6 and 12 months of the procedure. Endocarditis prophylaxis was recommended for the first 6 months after PFO occlusion. Patients were instructed to inform the operator of doubts or any procedure-related symptoms.

Statistical analysis

Data were entered into Microsoft Excel spreadsheets and analyzed using descriptive statistics. Categorical variables (patients, PFO and procedure characteristics) were expressed as absolute and relative frequencies. Quantitative variables were expressed as means and standard deviations, minimum and maximum values.

RESULTS

The mean age of patients was 48 years (range of 9 to 72 years) and 57% were males. Data collected are shown in table 1. Patent foramen ovale characteristics were as follows: IASA in 32 (6.0%) cases, and 9 (1.0%) had giant aneurysms (Figure 2).

Transcranial Doppler echocardiography revealed passage of large numbers of microbubbles in all patients (527). Shower or curtain pattern was detected in 465 (88%) of cases (Figure 3).

Successful percutaneous patent foramen ovale occlusion was accomplished in all patients (527). Fluoroscopy time was 6.8±3.0 minutes (range 2.8 to 19 minutes). Procedures were either TTE (6, 1.1%), ICE (131, 25%) or TEE (389; 73.9%). Amplatzer® and Occlutech® prostheses were implanted in 295 and 232 patients (56% and 44%, respectively; Table 1). There were no deaths and the following complications were observed: hematoma formation at the venipuncture site (three patients, 0.6%), femoral arteriovenous fistula with spontaneous resolution (two patients, 0.4%), cardiac tamponade resolved with drainage by pucture (two patients, 0.4%), intraprocedural supraventricular arrhythmia (22 patients, 4.2%), headache (27 patients, 5.1%) and AF (two patients, 0.4%) (Table 2). Large residual shunt requiring a second prosthesis was observed in two patients (0.4%). In another two patients (0.4%) a large residual shunt described in control echocardiography report was not confirmed

by catheterization or intraoperative echocardiography. However, physiological transpulmonary shunting was detected immediately after direct injection of microbubbles into pulmonary arteries. Ischemic stroke recurred in four patients (0.8%) over the course of 5 years. One patient (0.2%) required prosthesis removal 70 days after implantation due to hypersensitivity to nickel. Embolization or erosion were not observed.

Table 1. Characteristics of 527 patients, patent foramen ovale, and procedures performed

Variable	
Sex	
Female	226 (42.9)
Male	301 (57.1)
Age, years	
9-39	207 (39.3)
40-60	222 (42.1)
>60	98 (18.6)
Comorbidities	
DM	41 (7.8)
HTN	100 (19.0)
PFO characteristics	
Septal aneurysm	32 (6.1)
Gigant aneurysm	9 (1.7)
Passage of large numbers of bubbles	527 (100)
Shower or curtain pattern	465 (88.2)
Procedures	
Fluoroscopy, minutes	6.8±3.0 (2.8-19)
TTE	6 (1.1)
ICE	131 (25.0)
TEE	389 (73.8)
Type of prosthesis	
Amplatzer®	295 (56.0)
Occlutech®	232 (44.0)

Results expressed as n (%) or mean±standard deviation (minimum-maximum range). DM: diabetes mellitus; HTN: hypertension; PFO: patent foramen ovale; TTE: transthoracic echocardiography; ICE: intracardiac echocardiography; TEE: transesophageal echocardiography.

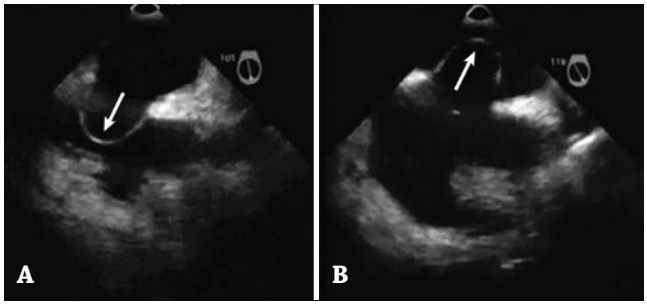

Figure 2. Large interatrial septal aneurysm (arrows).

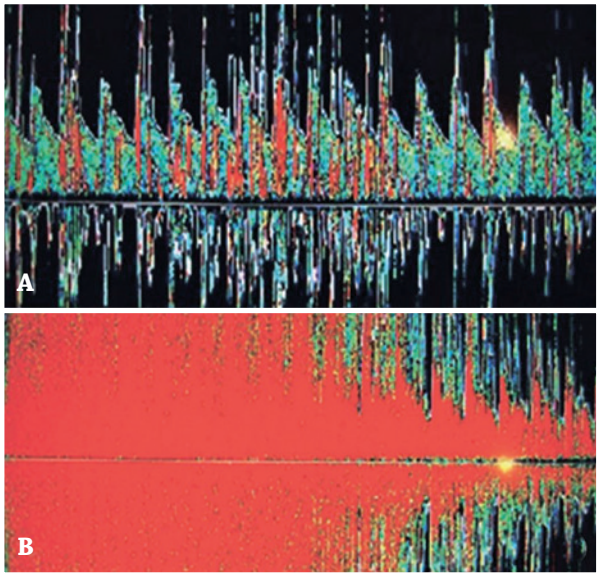

Figure 3. Transcranial Doppler. Shower pattern (A). Curtain pattern (B).

Table 2. Procedural complications

Complications	
Headache	27 (5.1)
Hematoma at venipuncture site	3 (0.6)
Femoral arteriovenous fistula	2 (0.4)
Cardiac tamponade	2 (0.4)
Transient SVES/PSVT	22 (4.2)
AF	25 (4.7)
During the procedure	23 (4.4)
In the first month	2 (0.4)
Residual shunt	5 (0.9)
Second prosthesis required	2 (0.4)
False-positive for residual shunt	2 (0.4)
Hypersensitivity to nickel*	1 (0.2)
Death, embolization or erosion	0
Recurrence of ischemic stroke†	4 (0.8)

Results expressed as n (%).
*Surgical removal on day 70; †5-year follow-up.
SVES: supraventricular extrasystole; PSVT: paroxysmal supraventricular tachycardia; AF: atrial fibrillation.

DISCUSSION

Paradoxical embolism via a PFO has been well described[10] and PFO occlusion is recommended by the American Heart Association (AHA).[3,12,13] The relation between PFO and ischemic stroke used to be a matter of controversy, since the prevalence of PFO is high (20% to 25% of adult population) and the incidence of ischemic stroke in patients with PFO is low (0.1%). It remains to be determined whether this is a mere coincidence or PFO occlusion is actually better to prevent secondary ischemic

stroke than drug treatment. High prevalence (over 40%) of PFO in patients with ischemic stroke relative to the prevalence reported in the adult population overall (20% to 25%)[3,12,13] drew attention to the role of PFO and the benefits of its occlusion.

With the advent of safe, user-friendly devices and the high rates of foramen occlusion with no residual shunt, increasing attention has been given to this topic in the last two decades. Several articles reporting on the efficacy of the method relative to drug treatment have been published.[14-19]

This series comprised exclusively patients with ischemic stroke and large shunts confirmed by ECHO and TDC. The procedure proved to be safe, with no patient mortality, low rates of residual shunt and no adverse events with potential complications for patients. As in other interventions, intraprocedural catheter-induced arrhythmia was often transient and promptly converted to sinus rhythm. Only 0.4% of patients progressed to AF.[18,20] One patient diagnosed with fibromyalgia complained of increasing pain following Occlutech® prosthesis implantation for PFO occlusion, and developed pericardial effusion two days after the procedure. Findings of CT angiography of the thoracic artery were unremarkable. The patient improved after treatment with non-steroidal anti-inflammatory drugs and clopidogrel (75mg/day) followed by maintenance therapy with ASA. However, after 3 weeks of treatment, generalized muscle pain persisted, despite pericardial effusion resolution. Transthoracic echocardiography and blood culture were repeated, with unremarkable findings. Treatment with prednisone was then initiated (40mg/day for 1 week followed by progressive dose reduction). Two months later, the patient was hospitalized due to persistent complaints of generalized discomfort and fatigue, and elevated C-reactive protein (PCR) levels. While in hospital, she was submitted to pulse methylprednisolone therapy for 72 hours and hypersensitivity testing using two Occlutech® prostheses attached to her arms. Nickel levels were also investigated. No skin reactions were noted and nickel levels were within normal ranges. Even with good overall health status, muscle pain and fatigue complaints and elevated CRP levels persisted. With the patient's consent, the prosthesis was removed. Given symptoms progressively subsided, and the clinical picture was associated to allergy to nickel. Lack of skin reactions in this case may be explained by corticosteroid therapy and improvement following prosthesis removal strongly suggests hypersensitivity to nickel.[21-23]

Another controversial issue is the indication of PFO occlusion as secondary prevention of ischemic stroke in patients aged 60 years, since ischemic stroke may be explained by the higher prevalence of other comorbidities in this age group. In this series, 89 patients (19%) were in this age range. These patients had no significant comorbidities and were diagnosed as high-risk PFO characterized by large right-to-left shunt, exuberant Eustachian valve and/or IASA. In these cases, events were monitored for 1 week to rule out paroxysmal AF. Patent foramen ovale occlusion was successfully achieved, with similar outcomes to younger patients. Intraprocedural AF occurred in a single older patient, with similar characteristics of AF seen in younger patients. This study revealed percutaneous PFO occlusion is a safe and effective procedure, regardless of patient age. In selected cases, patients aged over 60 years may benefit from percutaneous intervention. Therefore, these patients should not be excluded due to older age alone, as suggested by other authors.[20,24-29]

As to limitations, this is a retrospective study including data collected when PFO occlusion was a new procedure for most cardiologists. At that time, there were no studies to support the superiority of the method over medical treatment.

CONCLUSION

Percutaneous patent foramen ovale occlusion is a safe and effective alternative for secondary prevention of ischemic stroke. However, patients must be carefully selected, and other major causes of stroke ruled out. These measures combined with judicious characterization and quantification of right-to-left shunting and detailed anatomical study are key to successful outcomes. Patients aged over 60 years diagnosed as high-risk patent foramen ovale and no other potential causes of ischemic stroke may benefit from percutaneous occlusion, and should not be excluded due to older age alone.

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The authors declare there are no conflicts of interest.

CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: ECO; data collection: JAAB; data interpretation: ACLA; text writing: MFC and MCA; approval of the final version to be published: CMVF, JAAB and ECO.

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