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The percutaneous treatment of Patent Foramen Ovale, an effective and safe therapeutic choice

Research Article

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Abstract: Introduction. The aim of our study is to evaluate the feasibility, safety and efficacy of the percutaneous closure of PFO (abnormal communication between the right and left atrium). Methods. Between July 2009 and October 2012 percutaneous closure was performed in 37 patients. The presence of PFO was diagnosed through the use of ultrasound techniques: transcranial doppler with contrast (cTCD), transthoracic echocardiography(TTE) and transesophageal echocardiography (TEE). Follow-up was composed consisted of a Holter ECG 7 days after the closure with a 24 hour heart rhythm monitoring, to evaluate eventual arrhythmia cases and programmed controls which included a TTE at 1-3 months, TTE+ cTCD at 6-12 months, to evaluate the right positioning of the device and the complete closure of the defect. Results. We obtained 100% of procedural success (correct and stable implantation of the device in a perfect position on the interatrial septum).No complications were recorded during the procedure and no new onset atrial fibrillation was detected in any patients after the PFO closure. The follow up with cTCD and TEE reported a closing rate of 86.7%. No new clinical cerebrovascular events occurred in treated patients until now. Conclusion. Our experience describes the percutaneous PFO procedure as feasible, safe and effective with a high rate of procedural success, with an absence of significant adverse events and a high rate of complete closure.

Keywords: *Patent foramen ovale • Cryptogenic stroke • Percutaneous closure*

1. Introduction

Patent Foramen Ovale (PFO) is an abnormal communication between the right and the left atrium which persist in about 27% of the general population [1]. Numerous studies have demonstrated the association between patent foramen ovale and cryptogenic cerebral events: stroke or transient ischemic attack (TIA) [2-4]. In fact in particular hemodynamic conditions, it may allow the passage of emboli directly from the deep venous circulation to systemic circulation, through a mechanism of paradoxical embolism. This event can occur when the pressure in the right atrium exceeds that of the left atrium for example during the respiratory cycle or when the right atrium pressure increases due to coughing or Valsalva maneuver. Other clinical manifestations associated to PFO are decompression sickness in divers [5-7], and migraine with aura [8].

As PFO clinical management and the prevention of potential cerebral ischemic recurrence are still debated and unresolved matters. The aim of our study is to evaluate the feasibility, safety and efficacy of the percutaneous treatment of PFO closure in relation to secondary prevention of recurrent stroke events.

2. Patients and methods

Between July 2009 and October 2012, n=37 patients were treated by the percutaneous closure of PFO in our centre. The treated population is composed by 23

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females and 14 males. The age of patients ranges are from a minimum of 23 years to a maximum of 60 years (mean age 46 years±9,67).

The presence of PFO was diagnosed through the use of ultrasound techniques. Initially, the diagnosis of right to left shunt was achieved with bubble test with the transcranial doppler with contrast (cTCD–Figure 1). The exam involves the injection of agitated saline (9 ml of saline and 1 ml of air), which makes bubbles, into an antecubital vein to highlight the cerebral arteries, in particular the middle cerebral artery. Bubbles (MES–microembolic signals) highlighted into a cerebral artery during the first 3 cardiac cycles demonstrate the positivity of the test (Figure 1). Then a trans-thoracic echocardiography (TTE) was executed either in basal and during Valsalva maneuver, in order to confirm the right to left shunt of microemboli, found with cTCD. TTE also allowed the study of interatrial septum characteristics, showing its possible thinning, the presence of the interatrial septum aneurysm (ASA) and other anatomical anomalies such as the Chiari Network and the Eustachian Valve.

Patients which resulted positive at the cTCD and TTE tests were then subjected to a transesophageal echocardiography (TEE) with contrast to study better the anatomical and functional characteristics of PFO (Figure 2).

The shunt was divided into mild (n° 5 patients; 11.8%), moderate (n° 15 patients; 41.2%) and severe (n° 17 patients; 47%). The presence of ASA has been found in 56% of cases (19 patients) and in 3 patients it was recognized the presence of hyperechogenic structure due to embryonic residues.

Moreover, all patients had a genetic laboratory screening for thrombophilia (Factor V Leiden; Factor II; MTHFR) to evaluate eventual hypercoagulable state that can improve the risk of paradoxical embolism through a PFO.

Percutaneous treatment was executed, after these careful echocardiographic studies and neurological consults, in patients with occurrence of ischemic events TIA/ STROKE, classified as cryptogenic nature, often recurrent, or the presence of multiple cerebral ischemic lesions detected with magnetic resonance imaging (MRI), even if asymptomatic, for which no valid etiopathogenetic cause could be identified. Patients without ischemic lesions or patients with other possible causes of stroke, such as atrial fibrillation or carotid ultrasound plaques, were excluded. The 65% of treated patients had symptomatic cerebral ischemic events in their history.

The occurrence of any complications was investigated. Complications may be distinct in complications related to the procedure (bleeding, hematoma in the femoral access site, arterial-venous fistula, cardiac perforation with or without tamponade) and complications related to the device (thrombi on the device, infective endocarditis, rupture of the device, tissue erosion, explantation of the device for rejection).

3. Implanting procedure

The closure devices used up to now are: Amplatzer® (AGA Medical Corporation, Golden Valley MN, USA – in 4 patients 10.8%), Cardia® (Cardia Inc, USA – in 4 patients 10.8%) and Figulla® Flex Occlutech (Occlutech GmbH, Jena, Germany – in 29 patients 78.4%) – (Figure 3).

Before PFO closure all patient were informed about the procedure, the risks and the benefits; a cephalosporin antibiotic prophylaxis was done, followed by a recommendation for endocarditis prophylaxis for further 2-6 months.

The implanting procedure was executed with a femoral venous catheterization with local anaesthesia associated with mild sedation. A TEE or an intracardiac echocardiography ICE (9 MHz Ultra ICE, Boston Scientific Corporation, San Jose, California) were used to choose the appropriated device size and optimized the implantation (Figure 2), respecting anatomical relationships with other structures such as the aorta and the atrium roof.

At the end of the procedure, before removing the catheter, blood mixed with air used as a contrast, was injected during a Valsalva maneuver to evaluate the implantation result's and any possible residual shunt. At this stage residual shunt of bubbles is possible because the device is a dense mesh permeable which will become completely close only after about 6 months at the end of the process of re-epithelialization.

After percutaneous treatment all patients were treated with a double antiplatelet therapy with acetylsalicylic acid 100-325 mg/die and Ticlopidine 250-500 mg/die or Clopidogrel 75-150 mg/die for the first six months and then only acetylsalicylic acid 100-325 mg/die for 6 months more.

4. Follow-up

The follow-up is composed by a Holter ECG at 7 days after the closure, with a 24 hour heart rhythm monitoring to evaluate eventual arrhythmia cases after the device implantation. Afterwards programmed controls includes a TTE at 1 and 3 months, and TTE + cTCD at 6 months

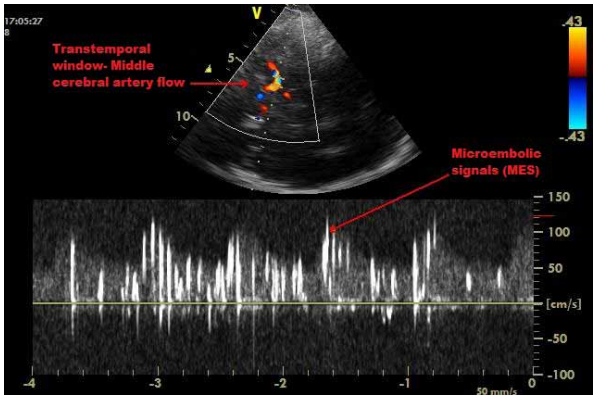

Figure 1. cTCD- microembolic signals (MES) in the middle cerebral artery.

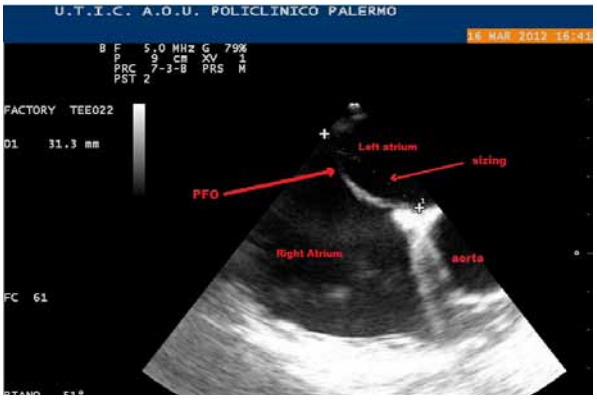

Figure 2. Sizing of the PFO (Transesophageal Echocardiography).

Figure 3. Figulla® Flex Occlutech device.

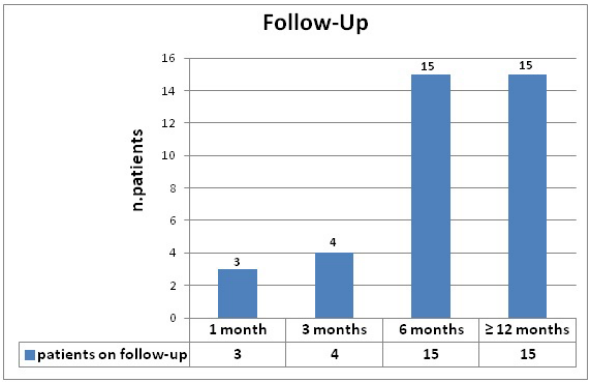

Figure 4. Patients on follow up (37 patients in total).

and 12 months (Figure 4), to evaluate the right positioning of the device and the complete closure of the defect. Subsequently patients are revaluated annually.

5. Results

In all our 37 closure we got a 100% of procedural success (correct and stable implantation of the device in a perfect position on the interatrial septum). No complications were recorded during the procedure nor complications concerning the device implantation. After the PFO closure only a case of hematoma in the femoral site was recorded. The presence of new onset atrial fibrillation (AF) was not detected in any patients after the procedure. The TTE performed at 1 and 3 months during follow up have been all favorable, testified by the correct position of the device in all patients. In addition, both new-onset aortic insufficiency and the exacerbation of already existing forms were excluded in all patients. Therefore, the device implantation did not interfere in any way with the functionality of aortic valve complex.

The follow-up with TTE + cTCD to our patients at 6 months (period of time during which more probably a complete re-epithelialization is made) has provided good results. They showed, in a large number of patients the achievement of a complete closure, as the device became an integral part of the interatrial septum.

In a total of 30 patients which have reached the 6 months follow up (4 patients with Cardia; 4 patients with Amplatzer; 22 of 29 patients with Figulla Flex), in only 4 cases were found a residual shunt (13.3%), with a closure rate of 86.7%.

Closure rate data at six months :

- Cardia closure rate 100%.
- Amplatzer closure rate 25% (3 patients resulted to have a residual shunt in a total of 4 patients);
- Figulla Flex closure rate 95.5% (Only 1 case of residual shunt; the patient didn't performed correctly and regularly the dual antiplatelet therapy after the PFO closure).

More important, after the execution of the closure procedure no cerebrovascular symptomatic events (stroke or TIA) occurred in treated patients, until now.

6. Discussion

Several data support the association between PFO and cryptogenic stroke [9-15], by a mechanism of paradoxical embolism, however PFO clinical management and the prevention of potential cerebral ischemic recurrences are still debated and unresolved matters [16-19]. Although studies suggest the superiority of the percutaneous treatment [20-23], these expectations have not been confirmed by the first multicenter, randomized clinical trial CLOSURE I [24] which compared percutaneous closure of PFO (n=447) using the Starflex ® device (NMT Medical, Boston, MA, USA) with the best medical therapy (n=462) in patients aged ≤ 60 years with cryptogenic stroke or TIA. Between the two treatment groups no significant differences in the incidence of stroke or TIA or in the primary combined endpoint (incidence at 2 years of stroke or TIA, all-cause mortality in the first 30 days, neurological mortality from 31 days to 2 years) were found. It was also underlined an increased incidence of atrial fibrillation in the group of patients treated with closure device compared to the group in medical therapy (5.7% vs 0.7%, respectively, P <0.001). This aspect, according to some authors may have contributed, in the percutaneous treatment group, to the finding of a stroke rate higher than expected [25]. Therefore, the presentation of the results of CLOSURE I indicates that PFO closure with Starflex ® device does not significantly reduces the rate of recurrent events compared to medical therapy, at a 2 years follow-up. However, several criticisms have been raised [25]. Several methodological reasons, in fact, may explain why the end points were not reached: a follow-up too short to demonstrate the benefits of PFO closure and to overcome the procedural complications; the imprecision of the inclusion criteria, stroke or cryptogenic TIA. However, before coming to conclusions about the most appropriate therapeutic approach in regard to the PFO treatment, it is necessary to await the results of appropriately designed studies with a longer follow-up period (CLOSE, CARDIA PFO Stroke Trial, PC Trial, RESPECT, REDUCE) comparing PFO closure with the best medical therapy.

In our centre the execution of the percutaneous technique has been initiated relatively recently. We attended to the 2010 Italian SPREAD (Stroke Prevention and Educational Awareness Diffusion) guidelines, evaluating case to case the most appropriated therapeutic choice for each patient, taking in consideration factors as the presence of multiple ischemic lesions, the presence of other cardiac abnormalities as ASA, the entity of the shunt, a history of deep venous thrombosis (DVT).

The results obtained from our follow-up are very encouraging, showing a high rate of complete closure 6 months after the application of the device, which becomes an integral part of the interatrial septum, and the absence of cerebral ischemic recurrences after treatment. To reach this result the medical support is essential, especially the months following the procedure, during which the complete closure of the PFO may not yet be reached. In this regard, we chose a dual antiplatelet therapy for first 6 months, followed by the administration of acetylsalicylic acid alone for other 6 months as a precaution.

Moreover, in order to obtain the highest probability of procedural success its very important to have a proper echographic support. In this regard, 16 procedures were performed with intracardiac ultrasound guidance and 21 with a transesophageal ultrasound. Despite the relatively higher costs, the intracardiac echocardiography (ICE) is certainly higher compared to the TEE, as it leads to numerous benefits. ICE in fact is far better tolerated by patients, with complete cooperation, and more important no sedation is required. Furthermore ICE does not stimulate the gag reflex, which is mostly produced instead by the ultrasound probe of TEE placed into esophagus. The gag reflex, is the most discomfort reaction which usually induces patients to do uncontrolled movements, which may represent an obstacle and a danger during the delicate procedure of the device implantation. That why sedation is often required during procedure with TEE. Therefore in this cases, the operator is deprived from the patient's precious cooperation, whereas if had been fully conscious, he could have make a good Valsalva maneuver, which is important to recognize the location and characteristics of the defect.

Certainly, further studies are necessary to define in symptomatic patients the optimal therapeutic strategy, adapting it to the specific risk profile as not all the PFO could be associated to the same risk of recurrent ischemic events [26,27].

7. Conclusions

Also our experience of percutaneous PFO closure describes the procedure as feasible, safe and effective. It also shows a high rate of procedural success, the absence of significant adverse events, and a high rate of complete closure of this interatrial septal defect.

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