Original Research

Percutaneous Closure of Atrial Septal Defects: Immediate and Mid-Term Results

Petros S. Dardas[1], Vlasis N. Ninios[1], Nikolaos E. Mezilis[1], Dimitrios D. Tsikaderis[1], Vasilis D. Thanopoulos[2]

[1]Department of Cardiology, St Luke's Hospital, Thessaloniki, [2]Department of Cardiology, Ag. Sofia's Children's Hospital, Athens, Greece

Introduction: The incidence of percutaneous closure of secundum atrial septal defects (ASD) and patent *foramen ovale* (PFO), which has become an established therapy, is constantly increasing. In this study, which is the first in the Greek literature, we present the immediate and mid-term results from this intervention in our center.

Methods: From April 2004 to April 2008, 103 patients underwent percutaneous closure of an ASD or PFO using Amplatzer closure devices. Thirty were male, the mean age was 37 ± 15.5 years, and the mean follow-up period 21.7 ± 14.8 months. The procedure was successful in 102 of the above patients; 69 (mean age 36.3 years ± 17.1, 81% female) underwent secundum ASD closure, while 33 patients (mean age 39.1 ± 10.5 years, 16 female and 17 male) underwent percutaneous closure of a PFO due to cryptogenic stroke.

Results: There were no major complications during the procedure (death, device embolization or need for immediate cardiac surgery). There were minor complications in 8 (7.7%) patients (bleeding at the puncture site, transient ST elevation in the inferior leads, multiple atrial and ventricular ectopics). The transient ST elevation in the inferior leads appeared in 5 patients (5%) and was probably due to air embolization. This transient complication completely resolved within 3 minutes. During the follow-up period, no patient had a major complication (cardiac rupture, device embolization, thrombus formation, thromboembolism or infective endocarditis). Most importantly, in the patients who underwent PFO closure there were no recurrences of cryptogenic stroke during the follow-up period (24.3 ± 14.5 months).

Conclusions: This study shows that using Amplatzer closure devices for atrial septal communications is both safe and effective, with sustained results over a maximum follow-up period of four years. Appropriate patient selection, as well as accurate device sizing fitting the dimensions of the defect, are important factors for the success and the safety of the method.

The incidence of percutaneous closure of secundum atrial septal defects (ASD) and patent *foramen ovale* (PFO), which has become an established therapy, is constantly increasing.[1] It is well known that patients who have suffered a cryptogenic stroke associated with PFO are at risk of recurrent stroke, despite being on medication.[2-5] The incidence of recurrence of the stroke in these patients varies from 0-15% per year.[6-9] This risk is particularly increased in patients with a combination of PFO and atrial septal aneurysm.[4,10,11] The likeliest mechanism of stroke in these patients is paradoxical embolization through the PFO.[12] It appears that percutaneous closure of the PFO is at least as effective as medication in preventing the recurrence of stroke. Moreover, the closure appears to be more effective than medication in patients who have suffered more than one event.[13] The only devices that have received FDA approval for percutaneous closure of ASD and PFO are the Amplatzer devices: Amplatzer

Septal Occluder and Amplatzer PFO Occluder (AGA, Medical Cooperation, Golden Valley, MN, USA). At present, these devices are the most commonly used devices for percutaneous closure of ASD[14] and the results are quite encouraging.[5,16] In this study, which is the first in the Greek literature, we present the immediate and mid-term results from using the Amplatzer devices in our center.

Methods

Patients

From April 2004 to April 2008, 103 patients underwent percutaneous closure of an ASD or PFO. Thirty were male, the mean age was 37 ± 15.5 years, and the mean follow-up period was 21.7 ± 14.8 months. All the patients underwent regular follow up. Written consent was obtained from every patient prior to the procedure.

Patients with ASD

The indications for closing the ASDs were: a) Sizable defects with shunt (Qp/Qs) >1.5/1; b) right heart volume overload; and c) development of symptoms. The patient selection for percutaneous closure was based on the morphology of the defect as well as the presence of a sufficient rim around it, particularly at the inferior and posterior parts of the defect. The assessment was performed using a transesophageal echocardiogram (TEE), either two-dimensional (2D TEE) or real time three-dimensional (RT 3D TEE) for the last 32 patients.

Patients with PFO

The indication for percutaneous PFO closure was the history of either isolated or recurrent cryptogenic stroke. The diagnosis of stroke was based on a sudden onset of symptoms or neurological signs and was confirmed by ischemic defects on computed tomographic scan or magnetic resonance imaging of the brain. A transient ischemic episode (TIA) was defined as a localized neurological event, with full recovery within 24 hours. All the patients underwent carotid and vertebral arterial Doppler, transcranial Doppler, electrocardiogram, transthoracic echocardiogram and TEE during performance of the Valsalva maneuver with intravenous agitated saline injection. The ischemic stroke was considered to be the result of paradoxical embolisation under three conditions: 1) presence of PFO, with or without the presence of atrial septal aneurysm, with either spontane-

ous or induced right to left shunting; 2) presence of stroke or TIA, confirmed clinically and angiographically; and 3) exclusion of other sources of emboli.

Diagnostic TEE protocol

In order to diagnose PFO, with or without atrial septal aneurysm, we used TEE (2D TEE and RT3D-TEE) and performed the Valsalva maneuver during infusion of agitated normal saline. The presence of atrial septal aneurysm was defined as the presence of excess tissue at the atrial septum, with excess motion greater than 10 mm from the right to the left atrium during the Valsalva maneuver.[10] The presence of either spontaneous or induced right-to-left shunt was calculated in semi-quantitative fashion, depending on the number of bubbles that were crossing through the defect to the left atrium: small (1-5 bubbles), moderate (6-20 bubbles) and severe (>20 bubbles).[17]

Amplatzer devices

Amplatzer septal occluder (ASO)

This device consists of two self-expanding disks made from a fine mesh of nitinol wire. These disks are connected by a short (4 mm) waist, whose diameter corresponds to the size of the ASD. The left and right disks are 14 mm and 10 mm larger, respectively, than the diameter of the waist. The device contains Dacron fibers to facilitate endothelization within the device. The ASO is available in sizes from 4-40 mm, which represent the diameter of the waist. It is advanced via the femoral vein through a long sheath available in sizes from 7-12 F. This device is attached to a 0.038" wire and inserted into a specialized short loading sheath.

Amplatzer PFO occluder (APFOO)

This device is a modification of the ASO. It consists of two disks made of nitinol. The connecting waist is shorter (3 mm). The right disk is larger than the left disk. During our study the APFOO was available in two sizes, 25 mm and 35 mm, which reflect the right disk diameter.

Implantation technique

The protocol of the implantation procedure has been described in detail in previous reports.[14] The procedure was performed under general anesthesia and under fluoroscopic and echocardiographic guidance.

We used TEE for size assessment and monitoring of the whole procedure. An intravenous bolus of 80 mg of gentamycin was administered 30 minutes prior to the procedure. The size of the ASO was determined using a specific catheter that is inflated through the defect under fluoroscopic and TEE guidance. In patients with PFO the size selected was mainly 25 mm. The 35 mm APFOO device was selected only for closing PFOs with an atrial septal aneurysm that was larger than 20 mm. Prior to releasing the device we performed a thorough examination to check the completeness of the occlusion. During the procedure, TEE was used to check the shape of the device, the possibility of thrombus formation either on or around the device, and the presence of residual or additional defects. We also examined the relationship of the device with adjacent structures, such as the atrioventricular valves, the pulmonary veins, the superior and inferior *vena cava*, and the coronary sinus. Once all these steps had been completed, the device was released from the loading wire.

Follow-up protocol

The patients received aspirin 3 mg/kg for 6 months until full endothelization of the device. Prior to discharge at 24 hours, they underwent ECG, chest X-ray and routine echocardiographic examinations. Two- and three-dimensional echocardiography was performed at the first, third, and sixth month of the follow-up period. Depending on the results of these examinations and on whether there were any other concerns, some patients underwent TEE. The patients were followed up regularly on an annual basis with clinical examination, ECG and echocardiogram. The patients who had had PFO closure were also followed by neurologists and underwent brain computed tomographic scan or magnetic resonance imaging if appropriate. All the patients were advised to take antibiotic prophylaxis for the first year after the procedure. Regarding the long-term management of the patients with PFO and cryptogenic stroke, we tend to recommend antiplatelet treatment for 6 months post procedure and then no antiplatelet therapy, unless there is an additional reason to continue on treatment, i.e. coronary artery disease, diabetes, thrombophilia. Close collaboration with the hematologists and neurologists is recommended.

Results

Results are expressed as mean ± standard deviation when appropriate.

Between April 2004 and April 2008, 103 patients underwent percutaneous closure of atrial septal communications. The procedure was successful in 102 of these patients: 69 patients (age 36.3 ± 17.1 years, 81% female) underwent secundum ASD closure and 33 patients (age 39.1±10.5 years, 16 female and 17 male) underwent percutaneous closure of a PFO due to cryptogenic stroke.

Patients with ASD

The maximum ASD diameter measured by TEE ranged between 18-35 mm (24 ± 0.7 mm). The diameter of the ASO ranged from 22-40 mm (27.7 ± 7.5 mm) (Table 1, Figure 1). We documented right heart dilatation and systolic pulmonary hypertension (>40 mmHg) in 47 patients and 21 patients, respectively. In one patient with secundum ASD it was not possible to close the defect because there was insufficient rim at the inferior-posterior border and the patient was referred for elective cardiac surgery.

Patients with PFO

Thirteen patients had atrial septal aneurysm (Figure 2), 9 and 14 patients had temporary and multiple (2-3) cerebrovascular events, respectively. Five patients were found to have a form of thrombophilia. The size of the device used was 25 mm and 35 mm in 24 and 9 patients, respectively (Table 2).

Periprocedural complications

2D TEE was performed in every patient (Figure 3) and RT3D TEE was performed in the last 32 patients (Figure 4) during the procedure. There were no major complications during the procedure (death, device embolization or need for immediate cardiac surgery). There were minor complications in 8 (7.7%) patients (bleeding at the puncture site, transient ST elevation

Table 1. Patients with secundum atrial septal defect.

Number of patients	69
Age (years)	36.3 ± 17.1
Gender	81% F (56/69), 19% M (13/69)
Right heart dilatation	68.1% (47/69)
Pulmonary hypertension > 40 mmHg	30.4% (21/69)
Maximum defect diameter	24 ± 7 mm
Device size	27.7 ± 7.5 mm
Months of follow up	22.1 ± 14.6
Transesophageal echo after 6 months	42% (29/69)
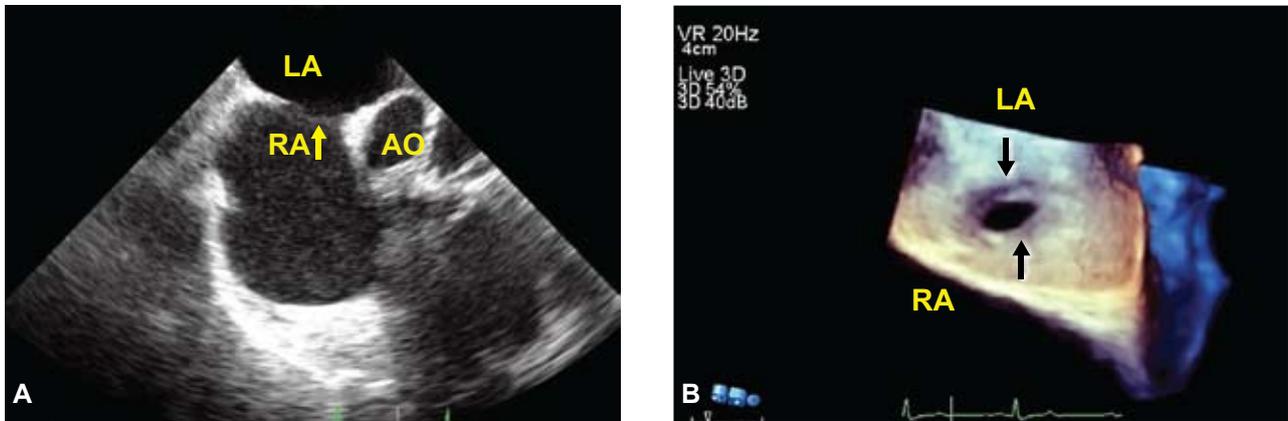
Figure 1. Two-dimensional (A) and three-dimensional (B) transesophageal echocardiograms showing an atrial septal defect (arrows) prior to percutaneous closure. LA – left atrium; RA – right atrium; AO – aorta.
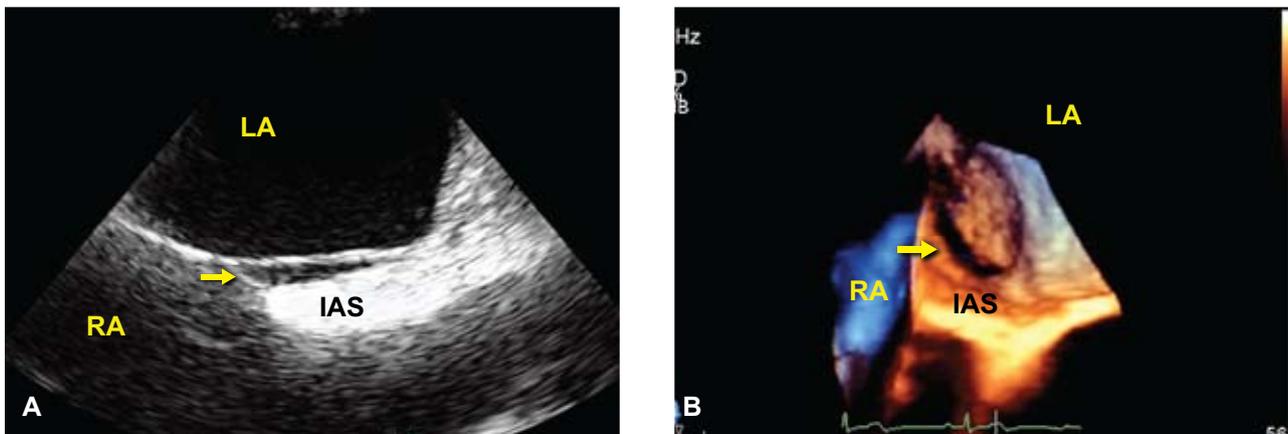
Figure 2. Two-dimensional (A) and three-dimensional (B) transesophageal echocardiograms showing a patent *foramen ovale* (arrow) prior to percutaneous closure. LA – left atrium; RA – right atrium; IAS – interatrial septum.

in the inferior leads, multiple atrial and ventricular ectopics). The transient ST elevation in the inferior leads appeared in 5 patients (5%) and was probably due to air embolization. This transient complication completely resolved within 3 minutes.

Follow up

During the follow-up period (21.7 ± 14.8 months), no patient had a major complication (cardiac rupture, device embolization, thrombus formation, thromboembolism or infective endocarditis). Most importantly, there were no recurrences of cryptogenic stroke in the patients who underwent PFO closure during the follow-up period (24.3 ± 14.5 months).

One patient had an increased frequency of paroxysmal atrial fibrillation episodes as well as moderate pericardial effusion, which occurred during the

Table 2. Patients with patent *foramen ovale*.

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Number of patients	33
Age (years)	39.1 ± 11.5
Gender	51.6% M (17/33), 48.4% F (16/33)
Associated atrial septal aneurysm	39.4% (13/33)
Transient ischemic attack	27.3% (9/33)
Multiple (>1) strokes	42.4% (14/33)
Thrombophilia	15.1% (5/33)
Device size	27.1 ± 3.8 mm
Months of follow up	24.3 ± 14.5
Transesophageal echo after 6 months	24.2% (8/33)

first 4 months following device implantation. She remained hemodynamically stable and her condition was treated as Dressler syndrome, with a short term steroid and colchicine course. We speculated that the symptoms might have been due to nickel allergy, although this was never confirmed. For the atrial fibrillation episodes she was given amiodarone. At
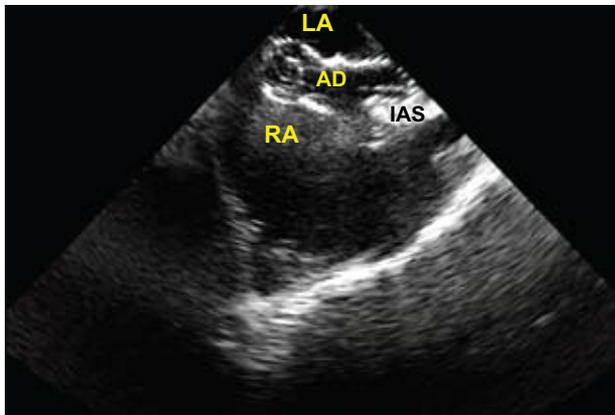
Figure 3. Two-dimensional transesophageal echocardiogram immediately following closure of an atrial septal defect. LA – left atrium; RA – right atrium; IAS – interatrial septum; AD – Amplatzer device.
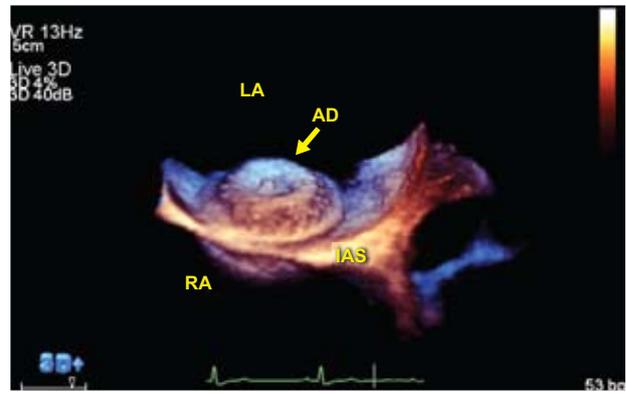
Figure 4. Three-dimensional transesophageal echocardiogram immediately following closure of an atrial septal defect. LA – left atrium; RA – right atrium; IAS – interatrial septum; AD – Amplatzer device.
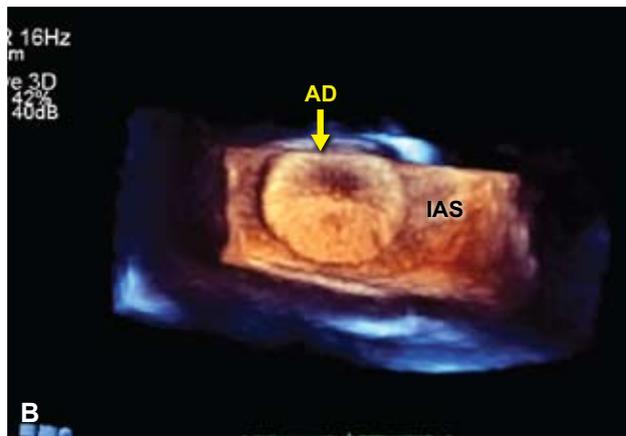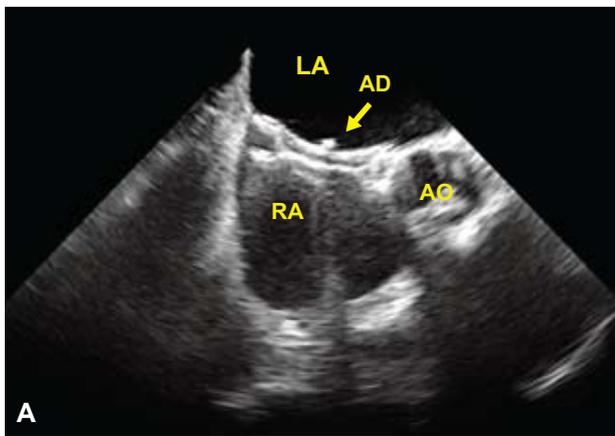
Figure 5. Two-dimensional (A) and three-dimensional (B) transesophageal echocardiograms 6 months after percutaneous closure. The endothelization of the device can be visualized on the 3D image. LA – left atrium; RA – right atrium; IAS – interatrial septum; AO – aorta; AD – Amplatzer device.

six months of follow up, the pericardial fluid had completely resolved and the patient had no further episodes of arrhythmias.

A transthoracic echocardiogram was recorded for every patient at six months' follow up and 37 patients (36.6%) also underwent TEE (Figure 5). During these studies, we checked the position of the device, particularly in relation to the tricuspid valve, the superior and inferior *venae cavae*, the pulmonary veins, and the coronary sinus. We looked for a possible residual shunt, for thrombus formation on or around the device, as well as possible deformation of the device. One patient had a slight deformation of the left atrial disk of the device immediately after implantation, which gradually resolved by the six-month follow-up echocardiogram. The remaining studies showed no pathological findings.

Discussion

This study clearly shows favorable immediate and mid-term results from using the Amplatzer devices for the percutaneous closure of atrial septal communications, which are consistent with similar results from other studies.

ASD closure

A recent study, which included 151 patients who underwent successful percutaneous closure of a secundum ASD, showed good long-term results (complete closure of the defect, with consistent results, free of death or significant complications, at three-year follow up).[18] A Canadian study published in 2005 showed a sustained improvement of left and right ventricular function following percutaneous closure,

as well as reduction of the left atrial size.[19] Another recent study, concerning the four-year follow up of 103 patients who underwent percutaneous ASD closure with Amplatzer device, showed a very low rate of immediate and long term complications.[20]

These results regarding percutaneous ASD closure are comparable with surgical intervention. In one non-randomized multicenter trial, comparing patients who underwent percutaneous closure (442 patients) versus surgical closure (154 patients), there was no statistically significant difference regarding the initial success rate. There was, however, a higher rate of immediate complications in the surgical group.[21]

The immediate complications following percutaneous ASD closure with an Amplatzer device are rare and involve mainly the very initial stage following the procedure.[16,22] Late complications are even rarer.[22-24]

There is an increased frequency of transient arrhythmias during the initial period following the implantation. This was observed in our patients; however, the arrhythmia burden was small and transient without any clinical consequences.[25]

There are case reports in the literature of device embolization, either early or late, due to suboptimal implantation technique.[26,27] This is mainly due to the use of a device that is too small for the size of the defect, or the lack of sufficient rim at the inferior-posterior defect border.

The rate of thrombus formation on Amplatzer devices is very low.[28,29] In our patient cohort we found no thrombus formation during the follow-up period. Nevertheless, since the TEE examination was not performed in all cases at six months' follow up, we might have missed some minor thrombi, clinically silent.

In this study, there were no late deaths during the follow-up period. There are rare case reports in the literature of cardiac rupture, which is of course a very ominous complication. There are also reports of fistula formation between the left and the right atria.[23,24] This is thought to be due to the use of an oversized device, which can cause rupture of the cardiac wall. Another recent study[30] showed a very small probability of myocardial erosion due to the device (0.1%). This is more likely to occur in patients with an ASD located near the aortic wall, as well as in patients with an oversized device. According to a different study,[31] cardiac perforation is usually observed during the immediate post-procedural period, but may occur up to three years later. However the probability of these complications is very low.

There were no signs related to infective endocarditis in our cohort. However, there is one case report of infection at two months' follow up; it is therefore considered imperative to provide antibiotic prophylaxis until full device endothelization, which usually occurs at twelve months.[32]

We had no incidence of atrioventricular valve dysfunction, *vena cava* obstruction, or obstruction of the outflow of the right pulmonary veins or the coronary sinus in our patients. However, we still consider it imperative to evaluate the anatomic relations of these structures with the device, using TEE prior to device release.

As mentioned above there was one case of device deformation immediately after implantation that was gradually restored during six months' follow up. This is in keeping with other reports[33] that temporary partial device deformation can occur but is gradually restored during the follow-up period.

PFO closure

There is good evidence that PFO may be linked with or be the cause of cryptogenic stroke. There are several observational studies with a documented increase in the frequency of PFO in patients with cryptogenic stroke (44-66% in patients with cryptogenic stroke vs. 9-27% in normal controls).[9,34-38] As a PFO is usually a tunnel, it has been speculated that the thrombus formation can actually take place within the PFO.[12,39-40] The recurrence of a cerebrovascular accident may also be related to the size of the PFO, as well as to the presence of an atrial septal aneurysm.[10,38,41-44] Mas et al also emphasized the increased likelihood of cerebrovascular accident recurrence in patients with a combination of a PFO and atrial septal aneurysm.[11]

The options regarding secondary prevention of stroke in patients with PFO include long-term use of antiplatelet or anticoagulant treatment, and percutaneous or surgical closure of the defect. There are several studies that show that medical treatment does not prevent stroke recurrence adequately.[8,9,45-46] Moreover, it is linked with an increased rate of bleeding complications, ranging from 2-15% per year in different studies.[9,45] So far, neither of the two treatment options, anticoagulation or antiplatelet treatment appears to be clearly superior to the other.[45] Surgical closure of the defect, on the other hand, is linked with increased morbidity, which is due to the thoracotomy.[34]

Several studies have shown that percutaneous

PFO closure in patients with cryptogenic stroke has a success rate ranging from 86-100%, with stroke recurrence from 0-4.9% per year.[13,34,47-53] A recent study found that percutaneous PFO closure in cryptogenic stroke is superior to conservative treatment in two patient groups: 1) patients with complete defect closure, and 2) patients with more than one stroke.[13] Another study, including 276 patients with PFO and cryptogenic stroke, showed that the recurrence rate of stroke after PFO closure with a device is very low (1.7% for transient ischemic attack and 0% for cerebrovascular accident). The follow-up period was 34 months.[48] A recent study by our group showed a clear superiority of percutaneous closure over medical treatment, regarding complications and stroke recurrence.[54]

Of course this evidence is based largely on observational non-randomized studies, and can therefore serve only for the formulation of hypotheses requiring proper trials. During the following months, the results of larger multicenter randomized trials (CLOSURE 1, RESPECT) are eagerly awaited to resolve the issue.

The complications of percutaneous PFO closure are relatively rare.[46,55,56] A recent study confirms that percutaneous PFO closure is a safe procedure with low rates of complications and recurrence of stroke.[57]

Completeness of defect closure

All of our patients had complete defect closure, with no residual shunt during the follow-up period. This is again consistent with previous studies that show high rates of complete defect closure during a follow-up period of up to three years.[16,18,58]

Conclusions

This study shows that using Amplatzer closure devices for atrial septal communications is both safe and effective, with sustained results over a maximum follow-up period of four years. Appropriate patient selection, as well as accurate device sizing to fit the dimensions of the defect, are important factors for the success and the safety of the method.

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