

Device-less patent foramen ovale closure by radiofrequency thermal energy

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Summary

The goal of this study was to assess the feasibility, safety and success of a system which uses radiofrequency energy (RFE) rather than a device for percutaneous closure of patent foramen ovale (PFO).

Methods: Sixteen patients (10 men, 6 women, mean age 50 years) were included in the study. All of them had a proven PFO with documented right-to-left shunt (RLS) after Valsalva manoeuvre (VM) during transoesophageal echocardiography (TEE). The patients had an average PFO diameter of 6 ± 2 mm at TEE and an average of 23 ± 4 microembolic signals (MES) in power M-mode transcranial Doppler sonography (pm-TCD), measured over the middle cerebral artery. An atrial septal aneurysm (ASA) was present in 7 patients (44%). Balloon measurement, performed in all patients, revealed a stretched PFO diameter of 8 ± 3 mm. In 2 patients (stretched diameter 11 and 14 mm respectively, both with ASA >10 mm), radiofrequency was not applied (PFO too large) and the PFO was closed with an Amplatzer PFO occluder instead. A 6-month follow-up TEE was performed in all patients.

Results: There were no serious adverse events during the procedure or at follow-up (12 months

average). TEE 6 months after the first RFE procedure showed complete closure of the PFO in 50% of the patients (7/14). Closure appeared to be influenced by PFO diameter, complete closure being achieved in 89% (7/8) with a balloon-stretched diameter ≤ 7 mm but in none of the patients >7 mm. Only one of the complete closure patients had an ASA. Of the remainder, 4 (29%) had an ASA. Although the PFO was not completely closed in this group, some reduction in the diameter of the PFO and in MES was documented by TEE and pm-TCD with VM. Five of the 7 residual shunt patients received an Amplatzer PFO occluder. Except for one patient with a minimal residual shunt, all showed complete closure of PFO at 6-month follow-up TEE and pm-TCD with VM. The other two refused a closure device.

Conclusions: The results confirm that radiofrequency closure of the PFO is safe albeit less efficacious and more complex than device closure. The technique in its current state should not be attempted in patients with a balloon-stretched PFO diameter >7 mm and an ASA.

Key words: patent foramen ovale; cardiac catheterisation; device-less closure; radiofrequency energy

Introduction

The patent foramen ovale (PFO) is an interatrial passage which is physiological before birth [1, 2]. Autopsies show that about 25% of the adult population have a patent foramen ovale (PFO) and that its presence decreases with age [1, 3]. PFO with intracardiac right-to-left shunt (RLS) can be identified by (transoesophageal) echocardiography (TEE) [4, 5] or power M-mode transcranial Doppler (pm-TCD). Both techniques require contrast agents and a Valsalva manoeuvre (VM) [6, 7].

The diagnosis, evaluation, and treatment of PFO have attracted increasing interest as the importance and frequency of its implication in several pathologic processes has been recognised.

PFO has been shown to be associated with ischaemic stroke [8–15] or myocardial [16] or renal infarction [17] secondary to paradoxical embolism, the platypnoea-orthodeoxia syndrome, decompression sickness [18], high altitude pulmonary oedema [19] and migraine headaches [20–24].

Several different PFO closure devices are in use today [25–32] which have virtually eliminated surgical PFO closure. Percutaneous closure systems provide excellent results and the implantation procedure is safe and simple. However, implanted devices carry a risk of early and mid-term problems [25–28, 30], such as thrombus, infection, device dislocation, transient arrhythmias [31–32] or wall erosion [33–35].

The periprocedural complication rates in studies evaluating percutaneous device closure of PFOs range from <1–10%. The most common periprocedural complications are air embolism (2%), ST-segment elevation (2%) or arrhythmia (2%) [31, 32]. Embolisation of the device is rare (1%). Late complications after device closure include arrhythmia (5–8%) [34], intracardial thrombus formation (3%) [31], device fracture (4%) or atrial wall erosion [33]. Recurrent transient ischaemic attacks occur in 2–4% [31, 32].

Pre-clinical animal studies have been performed to demonstrate the safety and feasibility of the PFX closure system using radiofrequency energy (RFE) in 29 pigs. A native PFO was present in 17 of the 29. RFE was successfully applied in all cases and 6 of the 7 PFO were closed. First degree atrioventricular (AV) block occurred in 2 of the 17 animals but there were no other complications [34, 35]. Histology was evaluated in 19 pigs at 6 weeks. All animals had healing fibrosis

and inflammation with complete endothelialisation of both right and left atrial surfaces without thrombus.

The first human study to demonstrate the safety and feasibility of the PFX closure system for the treatment of PFO was the Paradigm I study. Thirty patients were enrolled (15 females, 15 males, mean age 48 years). Mean PFO size was 8.5 ± 2.7 mm (stretched diameter). RFE application was achieved in 27 patients. The remaining 3 patients received an implantable closure device. Patients were free from serious adverse events. Thirteen of the 30 patients (43%) had complete PFO closure following the first procedure. Nine of the patients underwent a second procedure using RFE. Five of the 7 were closed following the second procedure, resulting in a secondary closure rate of 60% [36].

The purpose of the current study was to further assess the safety, feasibility, and technical success of the new system.

Methods

Patients

Inclusion criteria were age 18–65 years, PFO grade ≥ 2 (more than 6 crossed bubbles visible on a still frame of the left atrium), cryptogenic stroke (11 patients), divers with a history of diving incidents (1), or debilitating migraine (3).

Exclusion criteria were active infection, atrial thrombus, pregnancy, atrioventricular block, or atrial septal defect with left to right shunt. The study was approved by the Bern Ethics Committee, and all patients gave informed consent.

PFO closure technique

The PFX™-PFO closure system (CIERRA Inc. Redwood City, CA, USA) produces monopolar RF energy,

which denatures the tissue to the end of fusing the tunnel between the atrial septum secundum and septum primum at the level of the fossa ovalis, thereby closing the PFO. The procedure is carried out from the groin through the inferior vena cava and the right atrium. The metal electrode, which is connected to the RF generator, has a diameter of 15 or 19 mm. It has an elastomeric distal housing which covers the electrode.

An external generator produces the ablation energy. It monitors impedances and has an automatic shut down feature, germane to standard electrophysiology ablation equipment. As the energy is monopolar, a defibrillator pad is used as the return electrode. The procedure was carried out under TEE (Acuson Sequoia, Siemens, Erlangen, Germany) and fluoroscopic guidance. All patients

Figure 1

Left: Balloon measurement of a PFO in a 37-year-old woman representing a case for the technique. The marker distance of 15 mm is indicated. The tunnel measures 8 mm both in length and diameter.
Right: TEE aspect of the measuring balloon; LA = left atrium; RA = right atrium; B = balloon.

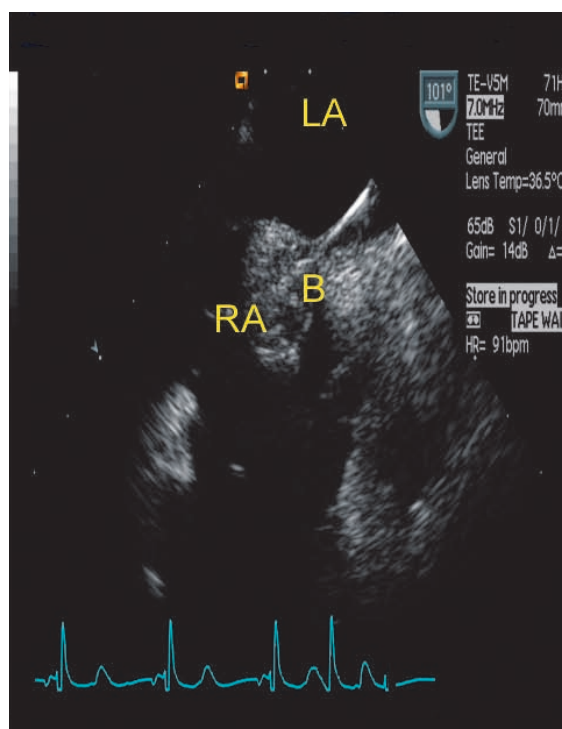
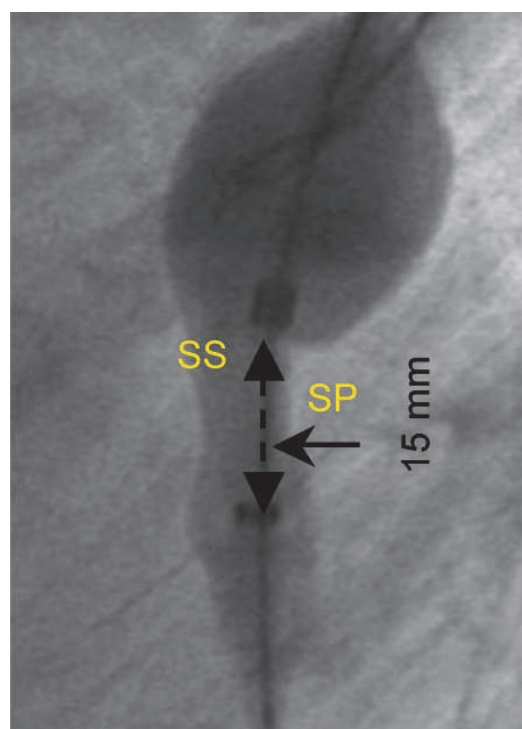


Figure 2

Left: Devices under suction during heat application adhering to both the septum secundum (SS) and septum primum (SP). C = RF catheter.
 Right: TEE aspect during heat application. SS = septum secundum; SP = septum primum; LA = left atrium; RA = right atrium; C = RF catheter.

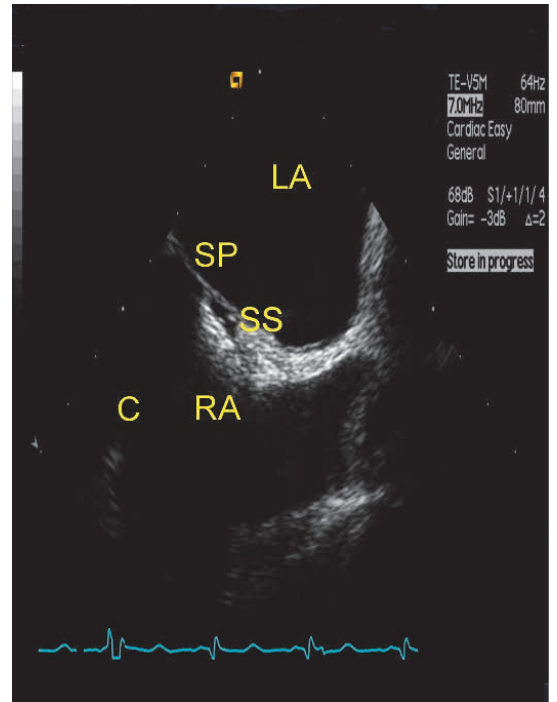
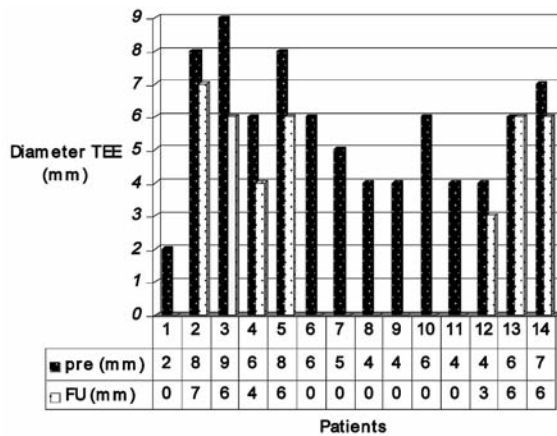


Figure 3

PFO diameters before (pre) the intervention and at 6 months (Fu).



were intubated under general anaesthesia during the procedure.

Prior to the PFO closure, the diagnosis of PFO was confirmed by contrast TEE. A multipurpose catheter was then inserted into the right femoral vein, and a guidewire passed through the PFO. A measuring balloon was passed over the guidewire and expanded with contrast media within the PFO to assess the PFO's stretched diameter to determine suitability for the procedure per protocol. Another TEE examination of the PFO without VM was repeated after the balloon measurement to exclude balloon induced anatomical changes.

A 16 French (5.5 mm) sheath was inserted into the patient's femoral vein to accommodate the PFx-15 closure system. The system was passed over the guidewire until it reached the PFO. Its position was monitored by TEE and fluoroscopy (fig. 1 and 2 left).

Once the position of the distal catheter was confirmed, suction was applied at the bell-shaped end of the catheter to hold the septum primum and secundum in place and united. In this stable position RFE was delivered via the catheter to close the PFO (fig. 1 and 2 right). RFE causes the tissue temperature to rise to about 40–60 °C which induces denaturation of collagens and proteins to weld the tissues of the septum primum and septum secundum together at the level of the fossa ovalis.

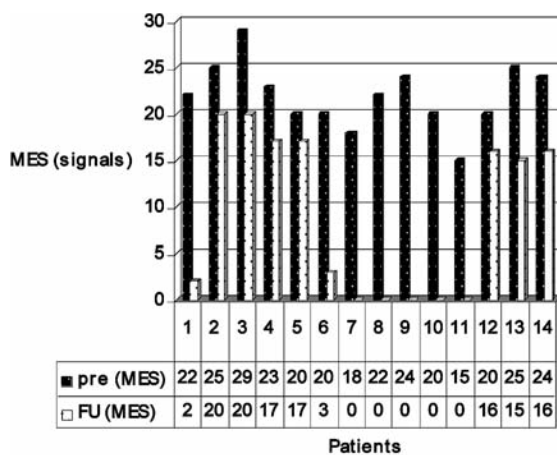
After completion of RFE application a TEE bubble study without VM was performed. The PFx closure system and the vascular access sheath were then removed, haemostasis was achieved using manual compression and the patients were extubated.

Follow-up

On the day following the intervention, a transthoracic echocardiography, a pm-TCD, and a 12-lead ECG were performed before discharge. All patients were instructed to take acetylsalicylic acid 100 mg daily for 1 month and clopidogrel 75 mg daily for 6 months. Follow-up examinations included a 12-lead ECG at 1, 3, 9, and 12 months after the intervention. Six months after the intervention TEE and pm-TCD were repeated to screen for a residual shunt.

Figure 4

Power M-mode transcranial Doppler device microemboli signals before (pre) the intervention and at 6 months (Fu).



Results

Patients

Between May and November 2006, 16 patients (mean age 50, range 21–75 years, 6 females) were enrolled in the study. All of them had a proven PFO grade >2 with documented RLS during VM. The patients had an average PFO diameter of 6 ± 2 mm at TEE with VM and an average of 23 ± 4 microembolic signals (MES) in pm-TCD measured over the middle cerebral artery

(Terumo Cardiovascular Systems Corporation, Ann Arbor, MI 48103, USA). Seven of the 16 patients (44%) had an atrial septal aneurysm (ASA) associated with PFO. The indications for PFO closure were secondary prevention of cryptogenic stroke ($n = 11$), diving incident ($n = 1$), or migraine headaches refractory to medical treatment ($n = 3$).

Intervention

Balloon measurement, performed in all patients, revealed a stretched PFO diameter of 8 ± 3 mm. Overall, the agreement between PFO diameters measured at TEE and during balloon sizing was 1:1.3.

Two of the 16 patients had to be excluded because their stretched PFO diameter measured by balloon sizing was >10 mm (11 and 14 mm) and the Pfx catheter was unable to seal successfully for suction. Both had an ASA. Their PFO were closed during the same procedure with a 25 mm and 35 mm Amplatzer PFO occluder respectively, with complete closure in 1 and 1 minimal residual shunt in the other at 6 months in TEE and pm-TCD during VM.

In the remaining 14 patients, the mean Pfx catheter time (from insertion to removal of the catheter) was 28 ± 12 (range 13–53) minutes. Mean duration of heat application was 8 ± 4 [7–11] minutes. Mean total fluoroscopy time was 8 ± 13 [8–32] minutes. Mean periprocedural blood loss resulting from vacuum suction during catheter positioning and RF application was 268 ± 251 (maximum 880) mL. No blood transfusions were required. During the intervention the ECG showed transient atrial arrhythmia in 3 patients (21%) and a transient ST-segment elevation (<2 min) in 1 patient (7%). Four patients (29%) had an inguinal haematoma (<10 cm) without clinical relevance. There were no further procedural complications.

PFO closure rate

The definition of the PFO closure rate was based on TEE 50% (7/14) rather than on pm-TCD 36% (5/14) in the 6-month follow-up examination. No differences of persistence of a right-to-left shunt were recorded early after the intervention and at the 1, 3, 6, and 12-month

follow-up examinations (TTE with pm-TCD at 1, 3 and 12 months and TEE with pm-TCD at 6 months).

The PFO closure rate was 89% (7/8) in patients with a balloon stretched diameter ≤ 7 mm, while closure was not achieved in any of the 6 patients with a diameter >7 mm. The mean PFO diameter of the 7 patients with successful closure by TEE had been 4 ± 1 mm with a balloon stretched diameter of 6 ± 2 mm. The mean MES had been 20 ± 3 signals in pm-TCD. Only 1 of these 7 patients had an associated ASA. The 7 patients with residual shunt at the 6-month TEE with pm-TCD evaluation had had a larger mean PFO diameter of 7 ± 2 mm (balloon stretched diameter of 9 ± 2 mm prior to the intervention) and 4 of them had an ASA. In pm-TCD an average of 24 ± 3 MES had been recorded in these patients before RF application. However, 6 months after RF application PFO diameter was reduced in these unsuccessful cases to 6 ± 2 mm, and only an average of 17 ± 2 MES were still recorded in pm-TCD. PFO closure with a 25 mm Amplatzer PFO occluder was performed in 5 of the 7 patients with residual shunt at TEE 6 months after the RF therapy. Except for one patient with a minimal residual shunt (grade 1), all of them showed complete closure at 6 months after the second procedure with TEE and pm-TCD. The two remaining patients refused device closure.

Clinical follow-up

During a follow-up of 12 ± 2 months there were no serious adverse events or recurrent embolic events. Two patients (14%) presented with transient atrial arrhythmia, 3 patients (21%) had a new first degree atrioventricular block and 2 patients (14%) a new partial right bundle branch block.

Discussion

This study confirms that PFO closure without device implantation by use of radiofrequency energy [34–36] is acceptably safe. There were no major procedural or follow-up complications. In general the reported events were comparable to those identified in the Paradigm 1 study using the same technique in larger studies evaluating implant devices [36].

However, despite the exclusion of patients deemed unsuitable for RFE closure and counting only residual shunts documented by TEE, the closure rate of PFO at the 6-month TEE was only 50% (in balloon-stretched diameter <7 mm 89%). The current maximum RFE application electrode size is 19 mm, which is apparently not suitable for larger PFO >7 mm (balloon-stretched diameter). Larger catheters are under development and could improve inclusion range and success. Notwithstanding, it will probably be more difficult to produce a tight seal for suction with them. The primary closure rates with current double-umbrella devices are as high as 90% [2]. Of the

7 RFE failures in the study who received an Amplatzer PFO occluder only 1 had a minimal residual shunt at follow-up compared with 9/14 with at least a minimal shunt in the RFE patients. Compared with device closure, RFE closure is of lower efficacy and more complex. Thus, despite the advantage of avoiding an implant, RFE closure is not competitive for PFO (balloon-stretched diameter) >7 mm pending refinement of the technique. PFO ≤7 mm (balloon-stretched diameter) involve little likelihood of paradoxical embolism.

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References

- 1 Kerut EK, Norfleet WT, Plotnick GD, Giles TD. Patent foramen ovale: a review of associated conditions and the impact of physiological size. *J Am Coll Cardiol.* 2001;38:613–23.
- 2 Meier B. Patent foramen ovale, guilty but only a gang member and for a lesser crime. *J Am Coll Cardiol.* 2006;47:446–8.
- 3 Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc.* 1984;59:17–20.
- 4 Fisher DC, Fisher EA, Budd JH, Rosen SE, Goldman ME. The incidence of patent foramen ovale in 1000 consecutive patients: a contrast transesophageal echocardiography study. *Chest.* 1995;107:1504–9.
- 5 Anzola GP. Clinical impact of foramen ovale diagnosis with transcranial Doppler. *Eur J Ultrasound.* 2002;16:11–20.
- 6 Spencer MP, Moehring MA, Jesurum J, Gray WA, Olsen JV, Reisman M. Power m-mode transcranial Doppler for diagnosis of patent foramen ovale and assessing transcatheter closure. *J Neuroimaging.* 2004;14:342–9.
- 7 Job FP, Ringelstein EB, Grafen Y, Flachskampf FA, Doherty C, Stockmanns A, Hanrath P. Comparison of transcranial contrast Doppler for the detection of patent foramen ovale in young stroke patients. *Am J Cardiol.* 1994;74:381–4.
- 8 Lechat P, Mas JL, Lascault G, Loron P, Thead M, Klimczac M, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med.* 1988;318:1148–52.
- 9 Wahl A, Kunz M, Moschovitis A, Nageh T, Schwerzmann M, Seiler C, et al. Long term Results after fluoroscopy guided closure of patent foramen ovale for secondary prevention of paradoxical embolism. *Heart* in print.
- 10 Schwerzmann M, Meier B. patent foramen ovale and stroke risk: the devil is in the detail. *J Am Coll Cardiol.* 2007;50:80.
- 11 Mas JL, Arquizan C, Lamy C, Zuber M, Cabanes L, Derumeux G, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med.* 2001;345:1740–6.
- 12 DeCastro S, Cartoni D, Fiorelli M, Rasura M, Anzini A, Zanette EM, et al. Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke.* 2000;31:2407–13.
- 13 Konstantinides S, Geibel A, Kasper W, Olschewski M, Blümel L, Just H. Patent foramen ovale is an important predictor of adverse outcome in patients with major pulmonary embolism. *Circulation.* 1998;97:1946–51.
- 14 Steinberg DH, Pichard AD, Satler LH, Slack MC, Wunderlich N, Majunke N, et al. Patent foramen ovale closure: past, present, future. *Expert Rev Cardiovasc Ther.* 2007;881–91.
- 15 Surmely JF, Meier B. Percutaneous closure of patent foramen ovale. *Minerva Cardioangiol.* 2007;55:681–91.
- 16 Mehan VK, Wahl A, Walpoth N, Meier B. Instant percutaneous closure of patent foramen ovale in patients with acute myocardial infarction and normal coronary arteries. *Catheter Cardiovasc Interv.* 2006;67:279–82.
- 17 Garachemani A, Eshtehardi P, Meier B. Paradoxical emboli through the patent foramen ovale as the suspected cause of myocardial and renal infarction in a 48-year-old woman. *Catheter Cardiovasc.* 2007;70:110–2.
- 18 Kerut EK, Truax WD, Borreson TE, Van Meter KW, Given MB, Giles TD. Detection of right to left shunts in decompression sickness in divers. *Am J Cardiol.* 1997;79:377–8.
- 19 Allemann Y, Hutter D, Lipp E, Sartori C, Duplain H, Egli M, et al. Patent foramen ovale and high-altitude pulmonary edema. *JAMA.* 2006;296:2954–8.
- 20 Tepper SJ, Sheftell FD, Bigal ME. The patent foramen ovale – migraine question. *Neuro Sci.* 2007;28:118–23.
- 21 Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke of for haemodynamic reasons. *Lancet.* 2000;356:1648–51.
- 22 Spies C, Schröder R. Transcatheter closure of patent foramen ovale in patients with migraine headache. *J Interv Cardiol.* 2006;19:552–7.
- 23 Schwerzmann M, Nedeltchev K, Meier B. Patent foramen ovale closure: A new therapy of migraine. *Catheter Cardiovasc Interv.* 2006;69:277–84.
- 24 Anzola GP, Magoni M, Guindani M, Rozzini L, Dalla Volta G. Potential source of cerebral embolism in migraine with aura. *Neurology.* 1999;52:1622–5.
- 25 Slavin L, Tobis JM, Rangarajan K, Dao C, Krivokapich J, Liebeskind DS. Five-year experience closure of patent foramen ovale. *Am J Cardiol.* 2007;99:1316–20.

- 26 Harms V, Reisman M, Fuller CJ, Spencer MP, Olsen JV, Krabill KA, et al. Outcomes after transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Am J Cardiol.* 2007;99:1312-5.
- 27 Windecker S, Wahl A, Chatterjee T, Garachemani A, Eberli FR, Seiler C, et al. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term. *Circulation.* 2000;101:893-8.
- 28 Billinger K, Ostermayer SH, Carminati M, DeGiovanni JV, Ewert P, Hess Jmaymone-Martins FA, et al. HELEX septal Occluder for transcatheter closure of patent foramen ovale: multicentre experience. *EuroIntervent.* 2006;465-71.
- 29 Anzola GP, Morandi E, Casilli F, Onorato E. Does transcatheter closure of patent foramen ovale really "Shut the Door?" *Stroke.* 2004;35:2140-4.
- 30 Martin F, Sanchez PL, Doherty E, Colon-Hernandez PJ, Delgado G, Inglessis I, et al. Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Circulation.* 2002;106:1121-6.
- 31 Braun M, Fassbender D, Schoen S, Haass M, Schraeder R, Scholtz W, et al. Transcatheter closure of patent foramen ovale in patients with cerebral ischemia. *J Am Coll Cardiol.* 2002;39:2019-25.
- 32 Wahl A, Krumdorf U, Meier B, Sievert H, Ostermayer S, Billinger K, et al. Transcatheter treatment of atrial septal aneurysm associated with patent foramen ovale for prevention of recurrent paradoxical embolism in high-risk patients. *J Am Coll Cardiol.* 2005;45:377-80.
- 33 Christen T, Mach F, Didier D, Kalangos A, Verin V, Trindate P. Late cardiac tamponade after percutaneous closure of a patent foramen ovale. *Eur J Echocardiogr.* 2005;6:393-5.
- 34 Hara H, Jones TK, Ladich ER, Virmani R, Auth DC, Eichinger JE, et al. Patent foramen ovale closure by radiofrequency thermal coaptation: first experience in the porcine model and healing mechanisms over time. *Circulation.* 2007;116:648-53.
- 35 Moore P, Feldman TE, Mead H, Hijazi Z, Rippey M, Richardson K, et al. Novel non-implant radiofrequency energy catheter closure of patent foramen ovale in swine. *J Am Coll Cardiol.* 2006;47(suppl A):249.
- 36 Sievert H, Fischer E, Heinisch C, Majunke N, Roemer A, Wunderlich N. Transcatheter closure of patent foramen ovale without an implant: initial clinical experience. *Circulation.* 2007;116:1701-6.

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