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Safety and feasibility of percutaneous closure of patent foramen ovale without intra-procedural echocardiography in 825 patients

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Abstract

Background: Percutaneous closure of patent foramen ovale (PFO) is generally performed using intra-procedural guidance by transoesophageal (TEE) or intracardiac (ICE) echocardiography. While TEE requires sedation or general anaesthesia, ICE is costly and adds incremental risk, and both imaging modalities lengthen the procedure.

Methods: A total of 825 consecutive patients (age 51 ± 13 years; 58% male) underwent percutaneous PFO closure solely under fluoroscopic guidance, without intra-procedural echocardiography. The indications for PFO closure were presumed paradoxical embolism in 698 patients (95% cerebral, 5% other locations), an embolic event with concurrent aetiologies in 47, diving in 51, migraine headaches in 13, and other reasons in 16. An atrial septal aneurysm was associated with the PFO in 242 patients (29%).

Results: Permanent device implantation failed in two patients (0.2%). There were 18 procedural complications (2.2%), including embolization of the device or parts of it in five patients with successful percutaneous removal in all cases, air embolism with transient symptoms in four patients, pericardial tamponade requiring pericardiocentesis in one patient, a transient ischaemic attack with visual symptoms in one patient, and vascular access site problems in seven patients. There were no long-term sequelae. Contrast TEE at six months showed complete abolition of right-to-left shunt via PFO in 88% of patients, whereas a minimal, moderate or large residual shunt persisted in 7%, 3%, and 2%, respectively.

Conclusions: This study confirms the safety and feasibility of percutaneous PFO closure without intra-procedural echocardiographic guidance in a large cohort of consecutive patients.

Key words: atrial septal aneurysm; patent foramen ovale; cerebral ischemia; embolism; secondary stroke prevention

Introduction

Percutaneous closure of the patent foramen ovale (PFO), first described in 1992 for secondary prevention of paradoxical embolism [1], is increasingly performed for a variety of indications [2]. In addition to secondary prevention of paradoxical embolism, [3–12] with non-randomized data suggesting an advantage over medical treatment [13, 14], refractory hypoxaemia due to right-to-left shunt in patients with right ventricular infarction or severe pulmonary disease, orthostatic desaturation in the setting of the platypnoea-orthodeoxia syndrome, neurological decompression illness in divers, and migraine with aura might constitute additional indications for PFO closure. The procedure is generally performed using simultaneous fluoroscopic and transoesophageal (TEE) [4, 6–9] or intracardiac (ICE) [15–17] echocardiographic guidance. While TEE requires sedation or general anaesthesia, and entails the risk of aspiration, ICE is costly and adds incremental risk to the procedure. Moreover, both imaging modalities considerably lengthen the procedure.

Conflicts of interest, financial disclosure: SW, HPM and BM: research grant and speaker bureau for AGA Medical

Methods

Patients

Between April 1994 and May 2006, 825 consecutive patients underwent percutaneous PFO closure at our institution. The interventions were solely guided by fluoroscopy, without intra-procedural echocardiography. The indications for PFO closure were presumed paradoxical embolism in 698 patients (95% cerebral, 5% other locations, see definition below), an embolic event with concurrent aetiologies in 47, diving in 51, migraine head-aches refractory to medical treatment as sole indication for PFO closure in 13, and miscellaneous other causes in 16. An embolic event was considered to be due to paradoxical embolism when the following criteria were fulfilled: presence of PFO with or without atrial septal aneurysm (ASA) with spontaneous or inducible interatrial right-to-left shunt during contrast TEE, clinically and/or radiologically confirmed ischaemic stroke, transient ischaemic attack, or peripheral embolism, and exclusion of any other obvious cardiac, aortic, or cerebrovascular cause. The procedure was approved by the local Ethics Committee, and patients gave written informed consent.

Echocardiography

The diagnosis of PFO and ASA was based on contrast TEE, with aerated colloid solution injected into an antecubital vein at the end of a vigorous and sustained Valsalva manoeuvre. PFO was defined as flap-like opening in the atrial septum secundum, with the septum primum serving as a one-way valve permitting permanent or transient right-to-left shunt. ASA was diagnosed as abnormally redundant interatrial septum with an excursion of ≥10 mm into the right or left atrium and a diameter of the base of the aneurysm of at least 15 mm [18]. Spontaneous or provoked right-to-left shunt was semi-quantitatively graded according to the amount of bubbles detected in the left atrium after crossing the interatrial septum on a still frame: grade 0 = none, grade 1 = minimal (1–5 bubbles), grade 2 = moderate (6–20 bubbles), and grade 3 = severe (>20 bubbles) [19]. Care was taken to document the actual passage of contrast bubbles through the rent but this was not possible in all cases. In three patients, the PFO suspected but not unequivocally demonstrated by contrast TEE was subsequently ruled out by angiography and mechanical probing.

Percutaneous PFO closure

The procedure was performed under local anaesthesia as described previously [3]. Intra-procedural guidance by TEE [4, 6–9] or ICE [15–17] was not used in any case. Of note, all patients were requested to undergo TEE prior to the intervention for initial diagnosis of PFO and detailed delineation of anatomy (ie associated ASA, Eustachian valve) including assessment of right-to-left shunt. Briefly, after venous access was gained via the right femoral vein, the PFO was crossed under fluoroscopic guidance in the anteroposterior view either by a standard length normal 0.035 inch guide wire alone, or with the help of a catheter, typically a 6 French Multipurpose catheter. Larger devices were selected in patients with ASA and larger shunts. Using Amplatzer PFO Occluders, a 25 mm device was selected for all cases save those with particularly low mobility of the interatrial septum (18 mm) or extremely high mobility or long funnel (35 mm). The device specific delivery system was then inserted over this wire. To keep the indwelling time of the sheath short, the device was prepared prior to this. Keeping the proximal sheath exit below heart level and the distal sheath exit away from the atrial wall, oozing through the sheath was ascertained before device insertion to avoid air embolism. After device deployment and upon verification of a correct position, [20] the device was released from the delivery cable (fig. 1). Finally, the sheath was removed and haemostasis achieved by manual compression, often done by the patient himself. Patients were released to full physical activity a few hours after the procedure, and treated with acetylsalicylic acid 100 mg once daily for five to six months for antithrombotic protection until full device endothelialization. The last 80% of patients also received clopidogrel 75 mg once daily for one to six months. A transthoracic contrast echocardiography was performed within 24 hours of percutaneous PFO closure in order to confirm correct and stable device position.

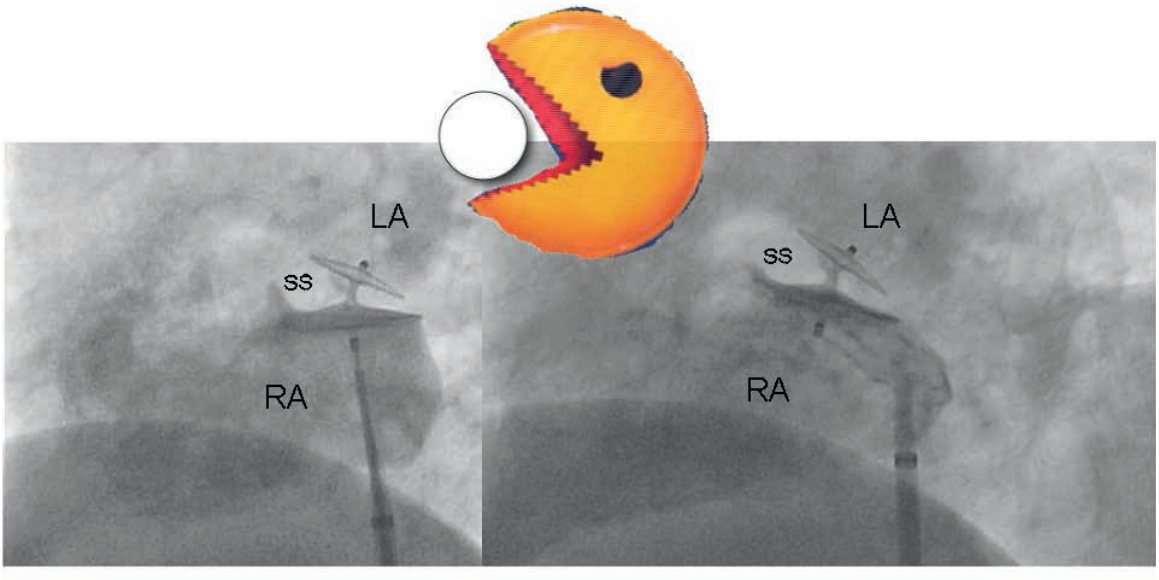

Figure 1

Pacman sign for documentation of correct position by fluoroscopy using a manual injection of contrast medium through the introducer. The thick muscular septum secundum (SS) is nicely depicted between the upper left halves of the device (25 mm Amplatzer PFO Occluder) looked at in perfect profile (usually a left oblique projection). This reminds of the arcade figure Pacman gobbling up a dot. Left: Pacman sign [20] before release from the delivery cable. Right: Pacman sign after release. RA = right atrium; LA = left atrium.

Follow-up evaluation

A contrast TEE was repeated six months after percutaneous PFO closure to assess for a residual shunt following endothelial overgrowth, and to exclude device malposition or thrombosis. In case of a significant residual shunt, a repeat TEE at one year was recommended. If a significant shunt persisted at that time, implantation of a second device was recommended.

Statistical analysis

Continuous variables are expressed as mean ± one standard deviation, and were compared by a two-sided, unpaired *t*-test. Categorical variables are reported as counts and percentages, and were compared by chi-square analysis. Statistical significance was assumed with a *p*-value <0.05. All data were analyzed with the use of SPSS software (version 12.0.1, SPSS Inc.).

Results

In-hospital outcome

Patient characteristics are summarized in table 1. A total of eight different atrial septal occlusion devices were implanted, selected per historical device availability and operator preference (table 2). Percutaneous PFO closure failed in two patients (0.2%) during our early experience. In one patient, a planned Sideris device was not used because of laceration of the femoral artery during initial insertion of an 11F venous sheath with an ensuing retroperitoneal haematoma. This required surgical revision, at which time the PFO was closed surgically. In another patient with PFO and a large ASA, an Amplatzer ASD Occluder was found embolized into the pulmonary artery twelve hours after the procedure. The device was retracted percutaneously into the femoral vein with an Amplatzer retrieval basket and removed from there by local incision. Repeat PFO closure was not attempted. Peri-procedural complications, including those described above, were observed in 18 patients (2.2%), and included embolization of the device or parts of it in five patients with successful percutaneous removal in all cases (two counter-occluder of Sideris devices, two PFO-STAR devices, one Amplatzer ASD Occluder), air embolism with transient symptoms in four patients (two PFO-STAR devices, one Angel-Wings, and one Amplatzer PFO Occluder), one transient ischaemic attack with visual symptoms in one patient (transient occlusion of a branch of the central retinal artery after implantation of an Amplatzer PFO Occluder), pericardial tamponade requiring pericardiocentesis in one patient (PFO-STAR) and vascular access site problems in seven patients (two Sideris, one PFO-STAR and four Amplatzer PFO Occluders). Five of the seven patients with vascular access complications had undergone simultaneous coronary angiography. There were no in-hospital deaths, and none of the procedural complications resulted in long-term sequelae.

Total procedure time, including incidental coronary angiography in 591 patients (72%), and ad hoc percutaneous coronary intervention in 41 (5%), was 45 ± 25 minutes (median 40 minutes). Total fluoroscopy time was 9 ± 8 minutes (median 7 minutes). In the last 100 cases with the Amplatzer PFO Occluder, total procedure time for PFO closure amounted to only 26 ± 11 minutes

Table 1
Baseline characteristics.

Patients	825
Age (years)	51 ± 13 (median 52; range 16–84)
Male gender	481 (58%)
Height (cm)	172 ± 9
Weight (kg)	75 ± 15
Body mass index (BMI, $kg.m^{-2}$)	25.2 ± 4.2
Atrial Septal Anatomy	
Left atrial size (mm)	37 ± 6
Patent foramen ovale only	583 (71%)
Patent foramen ovale and atrial septal aneurysm	242 (29%)
Cardiovascular Risk Factors	
Arterial hypertension	260 (32%)
Diabetes mellitus	39 (5%)
Smoking history	259 (31%)
Total cholesterol (mmol/l)	5.3 ± 1.1

Table 2
Implanted Devices (in order of first availability).

Device Type	**Patients n (%)**	**Total Procedure Time (min)**	**Fluoroscopy Time (min)**	**Procedural Complications (%)**	**Residual Shunt (%) Contrast TEE at 6 Months**
Sideris Buttoned Device	32 (4%)	71 ± 23	17 ± 8	13%	46%
Angel-Wings Occluder	10 (1%)	70 ± 20	12 ± 4	10%	10%
Amplatzer ASD Occluder	18 (2%)	73 ± 42	14 ± 8	6%	20%
CardioSEAL /STARFlex Septal Occluder	12 (2%)	71 ± 36	9 ± 6	0	9%
PFO-STAR/Cardia-STAR Septal Occluder	61 (7%)	55 ± 24	11 ± 6	10%	20%
Amplatzer PFO Occluder	683 (83%)	41 ± 23	8 ± 7	0.9%	10%
Helex Septal Occluder	1 (0.1%)	62	5.1	0	0%
Premere	8 (1%)	49 ± 21	13 ± 6	0	25%
Total	825			2.2%	12%

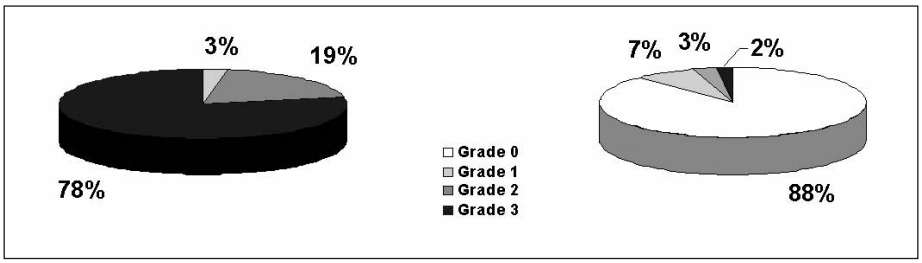

Figure 2

PFO-mediated interatrial shunt at baseline (left) and six months after percutaneous closure of patent foramen ovale (right), as assessed by contrast TEE. The grades are explained in the text.

(median 25 minutes) and fluoroscopy time was 4.1 ± 2.8 minutes (median 3.2 minutes).

Patients with occluder devices categorized as small (<30 mm; n = 701 patients) had less procedural complications as compared to patients with larger devices (≥30 mm; n = 121), ie 1.4% *vs* 6.6%, respectively (p <0.001). Patients with an associated ASA (n = 242; 29%) had similar device success (99.6% *vs* 99.8%; p = 0.52) and complication rates (2.1% *vs* 2.2%; p = 0.88) as compared with patients with an isolated PFO (n = 583; 71%). Patients ≥55 years (n = 348) and <55 years (n = 477) also had similar device success (100% *vs* 99.6%; p = 0.23) and complication rates (2% *vs* 2.3%; p = 0.78).

Transthoracic contrast echocardiography within 24 hours of percutaneous PFO closure detected a residual shunt in 15% of patients.

Late echocardiographic outcome

Complete PFO closure as assessed by contrast TEE at ≥6 months was achieved in 88% of patients, whereas a minimal, moderate or large residual shunt persisted in 7%, 3%, or 2% of patients, respectively (fig. 2). Patients with small occluder devices (<30 mm; n = 701 patients) had less residual shunts as compared to patients with larger devices (≥30 mm; n = 121), ie 10% *vs* 26%, respectively (p <0.001). Older (≥55 years; n = 348) and younger (<55 years; n = 477) patients had similar residual shunt rates (13% *vs* 12%; p = 0.55). Of note, contrary to previously reported observations by our group in a smaller cohort [10], patients with PFO and an associated ASA (n = 242; 29%) had somewhat higher residual shunt rates than patients with an isolated PFO (n = 583; 71%), ie 17% *vs* 10%, respectively (p = 0.02).

At the six month follow-up, contrast TEE examination showed a thrombus on the device in five asymptomatic patients. Three patients (one PFO-STAR, two Amplatzer PFO Occluder) had a small thrombus on the left atrial disc, which resolved after three months of oral anticoagulation. One patient (Amplatzer PFO Occluder) had a tiny thrombus on the left atrial disc, which remained unchanged after four months of oral anticoagulation. One patient had a 20 x 7 mm thrombus adherent to the right atrial disk (Amplatzer PFO Occluder) which resolved after six months of oral anticoagulation. Ten months after cessation of oral anticoagulants, TEE showed a recurrent right atrial thrombus, which resolved once again after oral anticoagulant therapy during six months, without further recurrences. The last echocardiography at seven year follow-up was normal. Hence, a thrombus at any time was seen in 0.6% of Amplatzer PFO Occluders, 1.6% of PFO Star devices, and none of the other devices.

A total of 23 patients (2.8%), with two Sideris, one Angel-Wings, two Amplatzer ASD, eleven Amplatzer PFO and seven PFO-STAR devices, underwent implantation of a second device (two Sideris, one CardioSEAL, two Amplatzer ASD and 18 Amplatzer PFO Occluders) due to a significant residual shunt. In all of these patients, TEE showed the initial closure device to be in the correct position, but demonstrated a residual shunt in the region of the former PFO. Several explanations are possible: The PFO may be incompletely covered by the device (like a pacifier placed in one edge of the toddler's mouth), or there may be a hitherto unrecognized second opening in the foramen ovale or one or several atrial septal defects. No peri-procedural complications occurred during the second intervention. After implantation of the second device, complete closure was finally achieved in 21 of 23 patients (91%). One patient treated with two Sideris devices had a minor residual shunt six months after the second intervention, which was no longer apparent at four years. One patient (Amplatzer ASD Occluder followed by Amplatzer PFO Occluder) had a minor residual shunt at six months, which persisted at two years. Another patient (two Amplatzer PFO Occluder 25 mm) still had a moderate residual shunt nine months after the second intervention.

In a patient with a PFO grade III associated with a large ASA, TEE two years after implantation of an Amplatzer PFO Occluder 35 mm (performed due to persistence of a residual shunt after six months) disclosed a new tiny atrial septal defect at the lower rim of the device, probably corresponding to an erosion of the interatrial septum due to the wear and tear of the ASA undulating incessantly between the right and left disc of the device. In another patient, routine TEE six months after implantation of an Amplatzer PFO Occluder 25 mm showed a completely occluded PFO, but a new small atrial septal defect was seen at the lower rim of the device. In both cases, these iatrogenic small atrial septal defects were successfully closed using an Amplatzer PFO Occluder 25 mm [21]. There were no further device related complications, in particular no erosions of the free atrial walls.

Discussion

The present study reports the safety and feasibility of percutaneous PFO closure in one of the largest series of consecutive patients treated at a single centre. Moreover, the procedure was performed without intra-procedural echocardiography in all patients. The principal findings are as follows. (1) Safety and feasibility of percutaneous PFO closure with the simple technique described above were confirmed in a large series. (2) Although device selection was not randomized, important differences were noted between the different PFO closure devices used. (3) Larger devices, usually selected for large shunts in the presence of an ASA, were associated with higher complication and residual shunt rates. (4) In patients with both PFO and ASA, which constitute a high risk population with a 3–5 fold increased risk for recurrent embolic events compared with patients with PFO alone [22], transcatheter treatment [10] might be associated with less recurrent events than secondary prevention with acetylsalicylic acid alone [23, 24]. In this series, an ASA associated with PFO had no influence on device success, nor on the risk of peri-procedural complications, but was associated with an increased residual shunt rate [5]. Concern has been raised that the current focus on cryptogenic stroke regarding indications for PFO closure may deprive the elderly who have the highest risk of paradoxical embolism [12, 25] of a simple preventive treatment [11, 26]. In this large series the procedure proved equally feasible and safe in selected older (≥55 years) and in younger patients.

Transcatheter treatment of patients with cryptogenic stroke and PFO has been shown to be safe and feasible using a variety of occlusion devices, mostly with [4, 6–9, 11] but also without intra-procedural echocardiographic guidance [3, 5]. Success rates varied between 90–100% of patients, complications were reported in 0–10%, and complete PFO closure in 51–100%. Routine TEE guidance provides little additional information to what can be gleaned from a hand injection of contrast medium [20] in a profile-adjusted view (fig. 1). TEE is poorly tolerated by the supine positioned patients, and therefore requires sedation or general anaesthesia, including intubation to virtually exclude the risk of bronchial aspiration, which considerably lengthens the procedure. ICE [15–17] is a costly alternative that is more comfortable for the patient, but it increases the invasive risk (rigid, unguided intravenous catheter). In this large series of PFO closure without intra-procedural TEE or ICE guidance, device success was close to 100% and the peri-procedural complication rate was 2.2%. Importantly, most complications occurred in our early experience with older devices [3]. This reflects both a learning curve and device improvements.

In the literature, the complete closure rates reported vary widely, from 51% to 100%. Obviously, the true residual shunt rate also depends on the technique used for assessment of residual shunts. In this study, complete PFO closure at six months, as assessed by contrast TEE at the end of a vigorous and sustained Valsalva manoeuvre, was achieved in 88% of patients. Most of the residual shunts were only minimal (1–5 bubbles), and thus likely to be missed by less sensitive techniques, such as colour Doppler TEE or transthoracic techniques. Although this series did not include a control group with echocardiographic guidance, both complication and residual shunt rates compare favourably with the published experience [1, 6, 8, 9, 11, 16]. Echocardiography was at beck and call during all procedures but never summoned. We feel that none of the complications could have been avoided by additional echocardiographic guidance. The success and complication rates depend on the device used [9, 10, 27]. In 683 patients receiving an Amplatzer PFO Occluder, device success was 99.6%, and the complication rate 0.9%. Since a residual shunt [3, 5, 10] and procedural complications were associated with recurrent embolic events, device selection is clinically relevant. While larger devices are easier to implant, and preferred by most operators in case of larger PFOs or associated ASAs, there are concerns about the risk of impairment or erosion of adjacent structures. On the other hand, smaller devices fit more snugly into the fossa ovalis, and may thus be more likely to completely close the PFO. However, they are more likely to embolize or to incompletely cover a slit-like PFO or a cribiform septum primum. In this non-randomized comparison most likely biased towards smaller devices (eg only 26% of patients receiving a smaller device had an associated ASA *vs* 50% for larger devices; $p < 0.001$), smaller devices (<30 mm) were associated with less complications and less residual shunts.

Limitations

Percutaneous PFO closure was performed using eight different device types during different time periods, according to historical device availability. Device allocation was non randomized and left to the discretion of the operator. However, baseline patient characteristics were similar between the different devices. Finally, it has to be remembered that the true therapeutic efficacy of percutaneous PFO closure as adjunct or alternative to medical treatment can only be ascertained by randomized studies, which have yet to be completed.

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References

1 Bridges ND, Hellenbrand W, Latson L, Filiano J, Newburger JW, Lock JE. Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. Circulation. 1992;86: 1902–8.
2 Wahl A, Windecker S, Meier B. Evaluation and treatment of abnormalities of the interatrial septum. Catheter Cardiovasc Interv. 2004;63:94–103.
3 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 risk of recurrent thromboembolic events. Circulation. 2000;101: 893–8.
4 Hung J, Landzberg MJ, Jenkins KJ, King ME, Lock JE, Palacios IF, et al. Closure of patent foramen ovale for paradoxical emboli: intermediate-term. J Am Coll Cardiol. 2000;35: 1311–6.
5 Wahl A, Meier B, Haxel B, Nedeltchev K, Arnold M, Eicher E, et al. Prognosis after percutaneous closure of patent foramen ovale for paradoxical embolism. Neurology. 2001;57:1330–2.
6 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.
7 Bruch L, Parsi A, Grad MO, Rux S, Burmeister T, Krebs H, et al. Transcatheter closure of interatrial communications for secondary prevention of paradoxical embolism: single-centre experience. Circulation. 2002;105:2845–8.
8 Braun MU, Fassbender D, Schoen SP, 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.
9 Braun M, Gliech V, Boscheri A, Schoen S, Gahn G, Reichmann H, et al. Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism. Periprocedural safety and mid-term follow-up results of three different device occluder systems. Eur Heart J. 2004;25:424–30.
10 Wahl A, Krumsdorf 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.
11 Kiblawi FM, Sommer RJ, Levchuck SG. Transcatheter closure of patent foramen ovale in older adults. Catheter Cardiovasc Interv. 2006;68:136–42.
12 Meier B. Patent foramen ovale, guilty but only as a gang member and for a lesser crime. J Am Coll Cardiol. 2006;47:446–8.
13 Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. Ann Intern Med. 2003;139:753–60.
14 Windecker S, Wahl A, Nedeltchev K, Arnold M, Schwerzmann M, Seiler C, et al. Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. J Am Coll Cardiol. 2004;44:750–8.
15 Koenig P, Cao QL, Heitschmidt M, Waight DJ, Hijazi ZM. Role of intracardiac echocardiographic guidance in transcatheter closure of atrial septal defects and patent foramen ovale using the Amplatzer device. J Interv Cardiol. 2003;16:51–62.
16 Onorato E, Melzi G, Casilli F, Pedon L, Rigatelli G, Carrozza A, et al. Patent foramen ovale with paradoxical embolism: midterm results of transcatheter closure in 256 patients. J Interv Cardiol. 2003;16:43–50.
17 Earing MG, Cabalka AK, Seward JB, Bruce CJ, Reeder GS, Hagler DJ. Intracardiac echocardiographic guidance during transcatheter device closure of atrial septal defect and patent foramen ovale. Mayo Clin Proc. 2004;79:24–34.
18 Pearson AC, Nagelhout D, Castello R, Gomez CR, Labovitz AJ. Atrial septal aneurysm and stroke: a transesophageal echocardiographic study. J Am Coll Cardiol. 1991;18:1223–9.
19 Webster MW, Chancellor AM, Smith HJ, Swift DL, Sharpe DN, Bass NM, et al. Patent foramen ovale in young stroke patients. Lancet. 1988;2:11–2.
20 Meier B. Pacman sign during device closure of the patent foramen ovale. Catheter Cardiovasc Interv. 2003;60:221–3.
21 Meier B. Iatrogenic atrial septal defect, erosion of the septum primum after device closure of a patent foramen ovale as a new medical entity. Catheter Cardiovasc Interv. 2006;68:165–8.
22 Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology. 2000;55:1172–9.
23 Mas JL, Zuber M. Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. Am Heart J. 1995;130:1083–8.
24 Mas JL, Arquizan C, Lamy C, Zuber M, Cabanes L, Derumeaux G, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med. 2001;345:1740–6.
25 Anderson FA, Jr., Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med. 1991;151:933–8.
26 Block PC. Patent foramen ovale closure in older patients: Have we been barking up the wrong tree? Catheter Cardiovasc Interv. 2006;68:143–4.
27 Schwerzmann M, Windecker S, Wahl A, Mehta H, Nedeltchev K, Mattle H, et al. Percutaneous closure of patent foramen ovale: impact of device design on safety and efficacy. Heart. 2004;90:186–90.

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