Five-Year Experience With Percutaneous Closure of Patent Foramen Ovale

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Patent foramen ovale (PFO) has been implicated in the pathogenesis of cryptogenic stroke, arterial desaturation, decompression illness, and migraine headache (MH). This study evaluated the safety of percutaneous transcatheter PFO closure in patients with cryptogenic stroke, transient ischemic attack, or arterial desaturation. Additionally, symptomatic reduction in MH was determined after interatrial shunt closure. Of the 252 patients referred to the University of California, Los Angeles, with PFO, 131 underwent closure of the interatrial communication with a CardioSEAL (n = 30) or Amplatzer (n = 101) device. PFO morphology was evaluated with transesophageal echocardiography. Follow-up was conducted at 1 to 2 months with echocardiography, with clinical assessment annually thereafter. At an average follow-up of 30 months, there was no recurrence of any thromboembolic event (transient ischemic attack, stroke, or peripheral). There was a reduction in MH, defined as the complete resolution of headache or a >50% reduction in the number of headache days, in 85% of patients after PFO closure. Temporary problems after device implantation, including chest discomfort and palpitations, were reported in 23% of patients and occurred more frequently in patients with nickel hypersensitivity (p < 0.05). In conclusion, transcatheter PFO closure is an effective and safe therapeutic modality in the prevention of thromboembolic events and MH associated with interatrial shunting in patients who present with cryptogenic stroke. Pending randomized, controlled trials are necessary to determine if this invasive approach is preferable to medical therapy for the prevention of recurrent stroke or as primary treatment for patients with MH.

Methods

**Patient population:** From April 2001 to April 2006, 252 patients were referred for consideration of percutaneous closure of PFO to the Interventional Cardiology Program at the University of California, Los Angeles. The primary reason for referral was history of cryptogenic stroke (n = 165) initially diagnosed by a neurologist. Cryptogenic stroke was defined by the presence of a transient or permanent neurologic deficit with associated magnetic resonance imaging (MRI) evidence of an embolic lesion in the absence of a clear cause. There were 43 patients (17.1%) referred with diagnoses of transient ischemic attack (TIA). These patients presented with transient focal neurologic deficits that lasted <24 hours in the absence of lesions on MRI. There were 16 patients (6.3%) referred for closure with significant arterial desaturation due to right-to-left shunt. There were 24 patients (9.5%) with primary diagnoses of MH (Table 1). Patients underwent diagnostic imaging of their head and neck vasculature with carotid ultrasound, computed tomographic angiography or magnetic resonance angiography, continuous cardiac monitoring, hypercoagulable workup (factor V Leiden, activated-protein C resistance, homocysteine, protein C, protein S, antithrombin III, lupus anticoagulant, β2-glycoprotein antibodies, anticoagulants, factor VIII, and prothrombin 20210A), and echocardiography. A prothrombotic state was determined on the basis of positive hypercoagulable laboratory workup results or a clinical predisposition such as malignancy or hormone replacement therapy. A total of 131 patients (52.0%) underwent percutaneous PFO closure. PFO closure was not performed for MH.

There are currently 2 randomized clinical trials evaluating whether the percutaneous closure of patent foramen ovale (PFO) can prevent the recurrence of cryptogenic stroke compared with anticoagulation or antiplatelet therapy. In addition, 4 randomized controlled trials will address the effectiveness of PFO closure in the management of migraine headache (MH). Patients with documented PFO and previous embolic events are at increased risk for recurrent stroke of up to 4.2% per year, even in the context of therapeutic anticoagulation. Percutaneous transcatheter closure is a potential option for patients with PFO and thromboembolic phenomena that avoids the morbidity associated with surgical closure or lifelong anticoagulation. However, long-term data on the effectiveness of transcatheter PFO closure in stroke prevention are limited. The present report details our 5-year experience with percutaneous transcatheter PFO closure for the prevention of recurrent stroke.

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Echocardiography: Transesophageal echocardiography (TEE) was performed using standard methods (TE-V5M, Acuson, Mountain View, California), and measurements were made using the Kinet-X echocardiographic imaging station (Siemens AG, Munich, Germany). An agitated saline bubble study was conducted to evaluate the degree of right-to-left shunt at rest and after the Valsalva maneuver. Patients received agitated saline injections into either the right-to-left shunt at rest and after the Valsalva maneuver. An agitated saline bubble study was conducted to evaluate the degree of right-to-left shunt at rest and after the Valsalva maneuver. The implantation technique for atherosclerosis, or PFO morphology in patients with adequate location of the device and to document the absence of residual shunt or thrombus formation on the device. Frequent clinical follow-up at 6- to 12-month intervals was performed with a questionnaire to evaluate symptoms, evidence of recurrent thromboembolic events, and the frequency and severity of MH. The Migraine Disability Assessment score was used to quantify the degree of disability. A subset of patients who received the Amplatzer device underwent testing with the Thin-layer Rapid-Use Epicutaneous (TRUE) skin test (Mekos Laboratories AS, Denmark) for nickel hypersensitivity.

Statistical analysis: Continuous data are presented as mean ± SD. The 2-tailed Student’s t test was used to determine the equivalence of the means for continuous variables. The chi-square test was used to determine equivalence for ordinal variables. Analysis was conducted using SPSS version 11.5 (SPSS, Inc., Chicago, Illinois). A p value <0.05 was considered significant.

Results

Patient characteristics: The clinical variables of the referred cohort and the PFO closure group are listed in Table 1. The primary reasons for referral included stroke in 165 patients (65.5%), TIA in 43 patients (17.1%), arterial desaturation in 16 patients (6.3%), and MH in 24 patients (9.5%). After evaluation, 20 patients were reclassified from the TIA group to the MH group on the basis of their clinical presentations, neurologic assessments, and MRI findings. The clinical data of the 2 groups are listed in Table 2. There were no significant differences in age, traditional risk factors for atherosclerosis, or PFO morphology in patients with TIA compared with those with MH. However, there was a

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**Table 1**

Clinical characteristics of patients referred for percutaneous transcatheter closure of patent foramen ovale

| Variable                              | Entire Cohort (n = 252) | PFO Closure (n = 131) |
|--------------------------------------|-------------------------|-----------------------|
| Mean age (yrs)                       | 50.0 ± 12.9             | 52.4 ± 13.5           |
| Women                                | 137 (54.4%)             | 65 (49.6%)            |
| Reason for referral                  |                         |                       |
| Embolic events                       | 208 (82.6%)             | 116 (88.5%)           |
| TIA                                  | 43 (17.1%)              | 13 (9.9%)             |
| Stroke                               | 165 (65.5%)             | 102 (77.9%)           |
| Arterial desaturation*               | 16 (6.3%)               | 13 (9.9%)             |
| MH†                                  | 24 (9.5%)               | 0 (0%)                |
| Other                                | 4 (1.6%)                | 3 (2.3%)              |
| Risk factors                         |                         |                       |
| Hypertension                         | 74 (31.2%)              | 39 (32.8%)            |
| Diabetes mellitus                    | 23 (9.5%)               | 14 (11.4%)            |
| Smoker‡                              | 30 (14.0%)              | 20 (19.2%)            |
| Hyperlipidemia§                      | 88 (37.3%)              | 45 (37.5%)            |
| Hypercoagulable predisposition       | 67 (42.9%)              | 32 (35.2%)            |
| Hypercoagulable state†              | 34 (21.8%)              | 20 (22%)              |
| Estrogen therapy¶                    | 33 (21.2%)              | 12 (13.2%)            |
| Incidence of MH                      | 109 (46.6%)             | 51 (42.9%)            |
| MH with aura                         | 94 (38.6%)              | 41 (38.4%)            |
| MH without aura                      | 15 (13.8%)              | 10 (19.6%)            |

* Refers to patients with either platypnea-orthodeoxia syndrome or refractory hypoxemia.
† Refers to patients with the primary diagnosis of MH.
‡ Refers to current smoking status or history of cigarette smoking.
§ Defined by the National Cholesterol Education Program Expert Panel.
¶ Hypercoagulable state was determined on the basis of laboratory workup (protein C, protein S, antithrombin III, factor V Leiden, prothrombin 20210A, factor VIII, homocysteine, anticardiolipin antibodies, β2-glycoprotein antibodies, and dilute Russell viper venom test.
¶¶ Refers to current smoking status or history of cigarette smoking.
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**Table 2**

Clinical characteristics of patients referred for patent foramen ovale with the diagnosis of transient ischemic attack or migraine headache

| Variable                              | TIA (n = 23) | MH (n = 48) | p Value |
|--------------------------------------|--------------|-------------|---------|
| Mean age (yrs)                       | 50.4 ± 9.1   | 45.7 ± 11.5 | 0.09    |
| Women                                | 13 (43.5%)   | 36 (75.0%)  | NS      |
| Hypercoagulable predisposition       | 4 (30.8%)    | 16 (72.7%)  | 0.025   |
| Hypercoagulable state*              | 2 (15.4%)    | 5 (22.7%)   | NS      |
| Estrogen therapy§                   | 2 (15.4%)    | 11 (50%)    | <0.05   |
| Hypertension                        | 8 (34.8%)    | 13 (28.3%)  | NS      |
| Diabetes mellitus                   | 1 (4.5%)     | 3 (6.3%)    | NS      |
| Smoker‡                             | 4 (18.4%)    | 7 (3.7%)    | NS      |
| Hyperlipidemia§                     | 10 (45.5%)   | 19 (39.6%)  | NS      |
| Aortic atherosclerosis§             | 4 (40.0%)    | 10 (55.6%)  | NS      |
| Carotid atherosclerosis¶            | 0 (0%)       | 2 (9.6%)    | NS      |

* Hypercoagulable state was determined on the basis of laboratory workup (protein C, protein S, antithrombin III, factor V Leiden, prothrombin 20210A, factor VIII, homocysteine, anticardiolipin antibodies, β2-glycoprotein antibodies, and dilute Russell viper venom test.
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significant increase in the number of patients receiving estrogen replacement (oral contraception or hormone replacement therapy) in the MH group (p < 0.05).

**Echocardiography:** TEE data were available in 82 patients (64.1%) from the PFO closure group and 37 patients (30.6%) without PFO closure. Table 3 lists the relevant PFO parameters from the PFO closure group and the nonclosure group. There were no significant differences in PFO parameters between the 2 groups. There were 18 patients (15.9%) with atrial septal aneurysms in the entire cohort. Analysis of the PFO morphology in patients with atrial septal aneurysms compared with those without demonstrated no significant differences in the PFO width or length or the width of the septum secundum between the 2 groups. The average bubble grade was greater in patients with atrial septal aneurysms (2.1 vs 1.7) but did not reach statistical significance (p = 0.12).

**Procedural outcomes:** Of the 131 patients who underwent percutaneous PFO closure, the Amplatzer device was used in 101 (77%) and the CardioSEAL in 30 (23%). The sizes of the Amplatzer devices used were 18 mm (n = 7), 25 mm (n = 49), and 35 mm (n = 44). The sizes of the CardioSEAL devices used were 23 mm (n = 7), 28 mm (n = 13), 30 mm (n = 1), 33 mm (n = 7), and 40 mm (n = 4). In 2 patients, 2 CardioSEAL devices were required to completely occlude the fenestrated septum. Procedural success was attained in 100% of patients with the 2 devices. Transseptal puncture was required in 10 patients (10%) in the Amplatzer group and 10 patients (33%) in the CardioSEAL group. Intra-cardiac echocardiography was used in 59 patients (45%), and TEE was used in 72 patients (55%). Procedural complications, including retroperitoneal hematoma, occurred in 3 patients (2%). One patient (3%) in the CardioSEAL group had a right coronary artery air embolism without clinical sequelae.

**Follow-up:** Follow-up TEE data were available in 104 patients (79%) at 1 to 2 months after the procedure. In the Amplatzer group, 10 patients (12.2%) had minor residual shunting, but no patient had a thrombus on the device. In the CardioSEAL group, 1 patient (5%) had residual shunting, and 6 patients (23%) had moderate thrombi on the devices, leading to 1 device explantation by surgery. Clinical follow-up at a mean of 30 ± 16 months (range 3 to 65) was acquired in 105 patients (80.2%). There were no recurrent episodes of embolic events (stroke, TIA, or peripheral embolization). Of the 131 patients who underwent PFO closure, there were 5 deaths (3.8%). The causes of mortality included metastatic pancreatic carcinoma (n = 1), septic shock (n = 2), ischemic cardiomyopathy (n = 1), and unknown (n = 1). There were no deaths caused by complications of the device. Minor adverse events, including chest discomfort (23%), palpitations (23%), and dyspnea (7%) were reported within a few weeks of the procedure. These symptoms disappeared after 1 to 3 months in most patients.

Of the 13 patients who underwent device closure for arterial desaturation, follow-up data were available in 9 patients. Three of the 13 patients died from underlying illnesses. There was symptomatic reduction in 5 patients (56%), with an average absolute increase of 7.5% on pulse oximetry (85.2 ± 4.1% to 92.7 ± 3.5%). The 4 patients (44%) without improvement on pulse oximetry did not report any symptomatic benefit.
Of the 50 patients (42%) in the PFO closure group who had MH, 40 (80%) had MH with aura, and 10 (20%) reported MH without aura. Tables 4 and 5 demonstrate the effect of percutaneous PFO closure on the incidence, frequency, and severity of MH. Postoperatively, MH disappeared completely in 30 of 47 patients (64%): in 25 of 37 patients (68%) with aura and in 5 of 10 patients (50%) without aura. A reduction in MH, defined as a >50% reduction in the number of headache days, was observed in an additional 10 of the 47 patients (21%): in 6 of 37 patients (13%) with aura and in 4 of 10 patients (40%) without aura. In total, 40 of 47 patients (85%) with MH had >50% reductions in the number of headache days. The average number of MH days during a 3-month period was significantly reduced, from 19.4 to 2.6 (p = 0.003). There was a significant decrease in the severity of MH, from 6.8 to 2.8 (on a scale ranging from 1 to 10; p <0.001). There was a concomitant reduction in the degree of disability, quantified by the Migraine Disability Assessment score, from 23.2 to 1.4 (p = 0.01).

Nickel sensitivity: The exacerbation of MH after device implantation in a patient who developed atrial fibrillation and pericardial effusion prompted an investigation of the association of nickel hypersensitivity and MH.15 The TRUE test for nickel sensitivity was conducted in 47 patients (46.5%) with the Amplatzer device; the results were positive in 8 (17%). The presence of MH was described by 5 of the 8 patients, all with aura, before PFO closure. Two of the 5 patients reported no reductions in their MHs. One patient without a history of MH developed MH with aura postoperatively that resolved after 6 months. There was a significant increase in the incidence of MH or palpitations (p = 0.025) and MH or chest discomfort (p = 0.05) in patients with nickel allergies.

Discussion

This retrospective analysis of 131 patients who underwent percutaneous closure with CardioSEAL or Amplatzer devices demonstrates the relative safety of percutaneous transcatheter PFO closure for patients who present with cryptogenic stroke. Over the course of 5 years, 252 patients were referred for PFO closure. The primary reason for referral was a history of embolic events in 208 (82.6%), defined by the clinical diagnosis of TIA or cryptogenic stroke confirmed by MRI. The association between PFO and cryptogenic stroke has been described from observational clinical trials.16,17 However, appropriate therapy for these patients is still undetermined. The rate of recurrent TIA and stroke in patients with cryptogenic stroke is estimated at 3.8% to 5.5% per year despite adequate anticoagulation or antiplatelet therapy.18–20 Some data also suggest that specific PFO parameters, such as the degree of right-to-left shunting, the presence of atrial septal aneurysm, and PFO tunnel length, may increase the risk for thromboembolic events and may represent the cohort of patients who will receive the greatest benefit from device closure.21,22

Of the 43 patients referred with the diagnosis of TIA, we suspect that 20 patients had complex MHs with transient neurologic deficits but no headaches. Differentiating between these 2 diagnoses remains a clinical dilemma because transient neurologic deficits such as paresthesia, hemiparesis, or aphasia can occur in patients with complex MHs.23–25 In the comparison of patients with MHs and TIAs, there was no significant difference in age, traditional risk factors, evidence of atherosclerosis, hypercoagulable states, or PFO parameters. There was a greater incidence of estrogen therapy in the MH group. We hypothesize that TIAs and MH may be causally related to the presence of a PFO. In 1 case, a small embolus passes through the PFO to produce a TIA, and in the second case, a chemical substance bypasses the lungs and enters the cerebral circulation to trigger the MH, with neurologic deficit that can occur with or without headache.15 If TIAs or complex MH cannot be distinguished clinically, it is difficult to justify PFO closure for a diagnosis of TIA alone with negative MRI results. However, if randomized, controlled trials demonstrate the safety and efficacy of PFO closure for MH, this distinction will be irrelevant from a practical basis. The corollary to this is the recognition that patients with MH have a 13% incidence of abnormal MRI findings.26 We hypothesize that these unidentified bright objects on MRI will be found to be associated with PFO and are the result of multiple small emboli. The 40% incidence of MH in patients with cryptogenic stroke is significantly greater than the 12% expected in the general population. We suspect that the higher rate of MH in patients with cryptogenic stroke and the higher rate of stroke in patients with MH are due to similar mechanisms, the right-to-left passage of chemical triggers or thrombus through a PFO or pulmonary shunt.

Previous trials with transcatheter PFO closure (a total of 538 patients) have documented a stroke or embolic recurrence rate of 0% to 3.2% at 1-year follow-up, depending on the device used.27–31 Studies involving the newer devices, including the Amplatzer PFO occluder, have demonstrated a rate of recurrence of <1% and an occlusion rate of 96% to 100%.28–31 Our experience revealed a 0% recurrence of embolic events in 115 patients with stroke who underwent PFO closure, with a mean follow-up of 30 months (range 3 to 65). Comparable with previous trials, there was a 100% procedural success rate, with a combined complication rate of 2%. The introduction of intracardiac echocardiographically guided implantation facilitates the procedure and is better tolerated than TEE. The frequency of residual shunting (10.8%) is greater compared with those found in previous studies.29–31 A potential explanation for this discrepancy is that most of the patients were evaluated by TEE at 1 month, as opposed to the 6 months used in other trials. One month may be an insufficient time for fibrous tissue formation to completely seal the septum.9 The significant increase in thrombus formation on the CardioSEAL device (23%) in comparison with the Amplatzer device (0%) led us to stop using the CardioSEAL device in 2003. The preferred use of the Amplatzer device may explain the 0% recurrent stroke rate. In our cohort, there was 0% perioperative mortality and 5 deaths (3.8%) during follow-up. These patients died from their underlying diseases, and none were associated with the implantation procedure, an inflammatory response to the device, or recurrent thromboembolic phenomena. If PFO closure is to be extended to otherwise healthy patients with MH, the procedural complication rate and the rate of emboli from the device must approach 0%.
Clinically, 23% of patients reported mild chest discomfort, and 23% reported palpitations that appeared 2 to 4 weeks after closure and resolved by 6 months. The presence of a foreign object within the heart stimulates an inflammatory response that could produce the chest discomfort and premature atrial complexes accounting for the palpitations. In addition, nickel allergy predisposes to an exaggerated inflammatory response, which can stimulate MH, presumably by releasing chemical triggers directly into the left atrium.

**Study limitations:** This study was a retrospective analysis and was therefore subject to selection bias. Another limitation is that echocardiographic data were not obtained at short- and long-term follow-up. The assessment of MH was conducted with an MH survey and disability assessment questionnaire, which is dependent on the patient’s subjective response, but these are the standard tools for assessing MH.

1. Chatterjee T, Petzsch M, Ince H, Rehders TC, Korber T, Weber F, Schneider H, Auf der Maur C, Niemaber CA. Interventional closure with Amplatzer PFO occluder of patent foramen ovale in patients with paradoxical cerebral embolism. *J Interv Cardiol* 2005;18:173–179.
2. Hanna JP, Sun JP, Furlan AJ, Stewart WJ, Sila CA, Tan M. Patent foramen ovale and brain infarct. Echocardiographic predictors, recurrence and prevention. *Stroke* 1994;25:782–786.
3. 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;130:1083–1088.
4. De Castro S, Cartoni D, Fiorelli M, Rasura M, Anzini A, Zanette EM, Beccia M, Collonese C, Fedele F, Fieschi C, Pandian NG. Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke* 2000;31:2407–2413.
5. Kerut EK, Nordfield WT, Plotnick GD, Giles TD. Patent foramen ovale: a review of associated conditions and the impact of physiological size. *J Am Coll Cardiol* 2001;38:613–623.
6. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497.
7. Braun MU, Fassbender D, Schoen SP, Haass M, Schraeder R, Scholtz W, Strasser RH. Transcatheter closure of patent foramen ovale in patients with cerebral ischemia. *J Am Coll Cardiol* 2002;39:2019–2025.
8. Van Camp G, Schulze D, Cosyns B, Vandenbossche JL. Relation between patent foramen ovale and unexplained stroke. *Am J Cardiol* 1993;71:596–598.
9. Sharafuddin MJ, Gu X, Titus JL, Uness M, Cervera-Ceballos JJ, Amplatzer K. Transvenous closure of secundum atrial septal defects: preliminary results with a new self-expanding nitinol prosthesis in a swine model. *Circulation* 1997;95:2162–2168.
10. Juc C, Wohlssein P, Bruegmann M, Zutz M, Franzbach B, Bertram H. A new biological matrix for septal occlusion. *J Interv Cardiol* 2003;16:149–152.
11. Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. *Cephalalgia* 1999;19:107–114.
12. Ale SI, Maibach HI. Reproducibility of patch test results: a concurrent right-versus-left study using TRUE test. *Contact Derm* 2004;50:304–312.
13. Ruiz CE, Alboliras ET, Pophal SG. The puncture technique: a new method for transcatheter closure of patent foramen ovale. *Catheter Cardiovasc Interv* 2001;53:369–372.
14. Anzai H, Child J, Watterson B, Krvikopack J, Fishbein MC, Chan VK, Tobis JM. Incidence of thrombus formation on the CardioSEAL and the Amplatzer interatrial closure devices. *Am J Cardiol* 2004;93:426–431.
15. Wertman B, Azarbal B, Riedl M, Tobis J. Adverse events associated with nickel allergy in patients undergoing percutaneous atrial septal defects or patent foramen ovale closure. *J Am Coll Cardiol* 2006;47:1226–1227.
16. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000;55:1172–1179.
17. Di Tullio M, Sacco RL, Gopal A, Mohr JP, Homma S. Patent foramen ovale as a risk factor for cryptogenic stroke. *Ann Intern Med* 1992;117:461–465.
18. Mas JL, Arquizan C, Lamy C, Zuber M, Cabanes L, Derumeaux G, Coste J. Patent Foramen Ovale and Atrial Septal Aneurysm Study Group. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm or both. *N Engl J Med* 2001;345:1740–1746.
19. Nedeltchev K, Arnold M, Wahl A, Sturzenegger M, Vella EE, Windecker S, Meier B, Mattle HP. Outcome of patients with cryptogenic stroke and patent foramen ovale. *J Neurol Neurosurg Psychiatry* 2002;72:347–350.
20. Bijl JM, Ryugrok PN, Hornung TS, Wilson NJ, West T. Percutaneous closure of patent foramen ovale. *Intern Med* 2005;35:706–710.
21. Agmon Y, Khandheria BK, Meissner I, Gentile F, Whisnant JP, Sicks JD, O’Fallon WM, Covalt JL, Wiebers DO, Seward JB. Frequency of atrial septal aneurysms in patients with cerebral ischemic events. *Circulation* 1999;99:1942–1944.
22. Windecker S, Wahl A, Nedeltchev K, Arnold M, Schwerzmann M, Seiler C, Mattle HP, Meier B. Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. *J Am Coll Cardiol* 2004;44:750–758.
23. Agostoni E, Aliprandi A. The complications of migraine with aura. *Neurolo Sci* 2006;27:59–65.
24. Buzzi MG, Moskovitz MA. The pathophysiology of migraine: year 2005. *Headache Pain* 2005;6:105–111.
25. Bousser MG, Welch KM. Relation between migraine and stroke. *Lancet Neurol* 2005;4:533–542.
26. Rocca MA, Ceccarelli A, Falini A, Colombo B, Tortorella P, Bernasconi L, Comi G, Scotti G, Filippi M. Brain gray matter changes in migraine patients with T2-visible lesions: a 3-T MRI study. *Stroke* 2006;37:1765–1770.
27. Onorato E, Melzi G, Cassilli F, Pedon L, Rigatelli G, Carrozza A, Maiolino P, Zanchetta M, Morandi E, Angeli S, Anzola GP. Patent foramen ovale with paradoxical embolism: mid-term results of transcatheter closure in 256 patients. *J Interv Cardiol* 2003;16:43–50.
28. Windecker S, Wahl A, Chatterjee T, Garachemani A, Eberli FR, Seiler C, Meier B. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: Long-term risk of recurrent thromboembolic events. *Circulation* 2000;101:893–898.
29. Du ZD, Cao QL, Joseph A, Koenig P, Heischmidt M, Waight DJ, Rhodes J, Brsonor J, Hijazi ZM. Transcatheter closure of patent foramen ovale in patients with paradoxical embolism: intermediate-term risk of recurrent neurological events. *Catheter Cardiovasc Interv* 2002;55:189–194.
30. Bruch L, Parsi A, Grad MO, Rux S, Burmeister T, Krebs H, Kleber FX. Transcatheter closure of interatrial communications for secondary prevention of paradoxical embolism. Single center experience. *Circulation* 2002;105:2845–2848.
31. Chatterjee T, Aeschbacher BC, Meier B. Ischemic attacks and patent foramen ovale: transcatheter closure of patent foramen ovale in adults with cryptogenic systemic embolism. *J Interv Cardiol* 1999;12:59–64.