REVIEW
DOI 10.4070/kcj.2008.38.12.631

Print ISSN 1738-5520 / On-line ISSN 1738-5555

Patent Foramen Ovale and Cryptogenic Stroke

Kook-Jin Chun, MD
Division of Cardiology, Department of Internal Medicine, Pusan National University Hospital, Busan, Korea

ABSTRACT

Patent foramen ovales (PFOs) are common congenital cardiac defects that have been associated with the occurrence of stroke, especially with cryptogenic stroke, or those of undefined cause, accounting for up to 40% of all ischemic strokes. A number of studies have demonstrated the association of larger PFOs with increased shunting in patients with cryptogenic strokes. Medical treatment is often considered inadequate, and percutaneous closure offers an attractive, albeit controversial, alternative in stroke patients with PFOs. Although it is plausible that percutaneous PFO closure will reduce the rate of recurrent stroke in these patients, no prospective, randomized trials examining the efficacy of closure devices in this setting have been completed. This paper reviews the known relationship between PFOs and cryptogenic strokes and discusses current therapeutic options, including percutaneous closure. **(Korean Circ J 2008;38:631-637)**

KEY WORDS: Patent foramen ovale; Stroke; Devices.

Introduction

A patent foramen ovale (PFO) is a remnant of the normal fetal circulation that can persist into adulthood. It was first described in 1564 by Leonardi Botali. The clinical significance of PFOs remained poorly understood for a long period of time. The advent of echocardiography allowed for the identification of PFO as a risk factor for several clinical syndromes, including ischemic stroke, myocardial infarction, decompression sickness in divers due to paradoxical embolism,[1-3] migraines, and platypnea-orthodeoxia syndrome.[4] PFOs are now amenable to interventional percutaneous therapy, and multiple novel technologies are either available or under development for lesion closure. This paper reviews the current knowledge of the relationship between PFOs and cryptogenic strokes and summarizes current therapeutic options.

Patent Foramen Ovale

PFOs are present in about a quarter of the adult population. The prevalence may decline with age. However, PFOs increase in size with age. This trend may reflect size selection as larger defects remain patent while smaller defects close spontaneously.[5]

Correspondence: Kook-Jin Chun, MD, Department of Internal Medicine, Pusan National University Hospital, 1-10 Ami-dong, Seo-gu, Busan 602-739, Korea
Tel: 82-51-240-7228, Fax: 82-51-240-7796
E-mail: ptca82@hotmail.com

PFOs are residual, oblique, slit-shaped defects resembling tunnels, which normally close secondary to the formation of fibrous adhesions between the septum primum and secundum during the first months of life. These adhesions help to form a valve-like structure, with the "door-jam" located in the left atrium (LA) side of the atrial septum.[5][6] After birth, the increase in pulmonary blood flow and rising LA pressure push the septum primum rightward against the septum secundum, shutting the flap of the PFO. Flap fusion is complete by age two years in 70 to 75 percent of children, with the remaining 25 to 30 percent having a PFO. When right atrium (RA) pressure rises intermittently with Valsalva or other isometric strain, the leaflets of the PFO may separate, resulting in leftward excursion of the septum primum and permitting flow from the RA to the LA (Fig. 1).

PFOs are associated with other cardiac anomalies, including atrial septal aneurysms (ASAs) and Chiari networks.[7] ASAs consist of redundant congenital atrial septal tissue in the region of the fossa ovalis, bulging into the RA or LA during respiration. The prevalence of ASAs is 1% in autopsybased studies, a number differing from echocardiographic studies.[7][8] One adult study showed that 33% of patients with ASAs also had PFOs, although 32% had isolated ASAs.[9] The odds of having a PFO are 4.6 times greater in patients with ASAs than in those without ASAs. ASAs are more frequent in stroke patients, but they are also more common in patients with PFOs, making cause and effect uncertain.

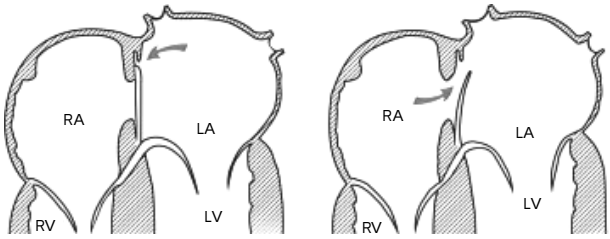

Fig. 1. Schematic representation of the interatrial septum. After birth, there is a functional closure of the foramen ovale because left atrial (LA) pressure exceeds right atrial (RA) pressure (left). Usually, a permanent seal develops. In patients with a patent foramen ovale (PFO), the seal does not fully develop, allowing blood to flow from the RA to the LA if RA pressure rises, such as is seen with Valsalva maneuver. LV: left ventricle, RV: right ventricle.

Cryptogenic Stroke

Cryptogenic stroke refers to an ischemic cerebrovascular accident (CVA) that occurs in the absence of significant risk factors or clear cause. The majority of ischemic strokes are due to cardioembolism, large vessel atherothromboembolism, small vessel occlusive disease, or other mechanisms. Cryptogenic strokes account for 30 to 40 percent of all ischemic strokes.[10] The risk factors for cryptogenic stroke are not clearly different from the risk factors for other types of ischemic stroke, although hypertension may be less common in patients with cryptogenic stroke compared to those with other types of ischemic strokes. The pathophysiology of cryptogenic stroke is likely heterogeneous, and proposed mechanisms include paradoxical embolism from atrial septal abnormalities such as PFOs, occult cardiac embolism secondary to aortic atheromatous disease or other cardiac sources, hypercoagulable states, preclinical or subclinical cerebrovascular disease, and inflammatory processes.

Patent Foramen Ovale and Cryptogenic Stroke

The relationship between paradoxical (right-to-left) embolism through a PFO and stroke remains controversial because of variability in the reported stroke risk in patients with PFOs.[2][11-14] PFO itself may be an innocent bystander or etiologic mechanism involved in paradoxical embolism, especially in patients younger than 55 years of age.[15] The clinical diagnosis of paradoxical embolism is presumptive and based on the absence of a left-sided thromboembolic source, a right-to-left shunt, and optionally, the detection of thrombus in the venous system or right heart chambers. The proposed CVA mechanism entails paradoxical embolism, with passage of thrombi from the peripheral venous system to the left cardiac cavities through a septal defect after Valsalva maneuver. Thrombus formation in the atria as a consequence of possible atrial arrhythmias is often associated with PFOs.[16] Thrombus formation within the PFO tunnel secondary to blood stasis inside the tunnel and hypercoagulability is associated with PFO.[17][18]

A number of case-control studies have reported an increased prevalence of PFO and ASA in patients with a history of cryptogenic stroke.[8][9][19-24] A meta-analysis of these case-control studies found that the presence of a PFO, ASA, or both was significantly associated with ischemic stroke in patients <55 years of age {odds ratios (OR) 3.1, 6.1, and 15.6, respectively}.[15] By comparison, the association in patients over the age of 55 was less certain (OR 1.3, 3.4, and 5.1, respectively). However, a recent prospective analysis showed that concurrence of PFO and ASA is a high-risk characteristic in older patients, as well.[25]

The Patent Foramen Ovale and Cryptogenic Stroke Study (PICSS) prospectively followed 630 patients.[26] The patients were randomly assigned to receive either aspirin (325 mg/day) or warfarin {mean international normalized ratio (INR) 2.04}. In this cohort, 265 patients (42%) had experienced a cryptogenic stroke in the past; on transesophageal echocardiography (TEE), the patients with a history of cryptogenic stroke had a higher rate of PFO than those with a known cause of stroke (39 versus 29%) and a significantly higher rate of large PFO (20 versus 9.7%). The overall incidence of ASA was 11.5%, but the incidence in patients with PFOs was not given. Among all patients in PICSS, no association was found between the presence of PFO alone and recurrent stroke or death. There was also no association between concurrent PFO and ASA and recurrent stroke or death. Among those patients with cryptogenic stroke, the two-year risk of recurrent stroke or death was not significantly different between those with PFOs (14.3%) and those without PFOs (12.5%). Moreover, there was no evidence of reduction in risk among those cryptogenic stroke patients with PFOs assigned to the warfarin group (hazard ratio 0.52, 95% CI 0.16-1.67).

The Northern Manhattan Stroke Study (NOMAS) prospectively evaluated 1,100 stroke-free subjects 40 years of age or older (mean age 69 years) from Manhattan using transthoracic echocardiography to look for the presence of PFOs and ASAs.[27] PFOs were detected in 14.9 percent of subjects, and ASAs were detected in 2.5 percent. During a mean follow-up period of 80 months, ischemic strokes occurred in 68 subjects. PFO was associated with a statistically insignificant increase in stroke risk {hazard ratio (HR) 1.64, 95% CI 0.87-3.09}, as was the coexistence of PFO and ASA (HR 1.25, 95% CI 0.17-9.24).

The Stroke Prevention: Assessment of Risk in a Community (SPARC) study prospectively evaluated 588 ran-

domly sampled subjects 45 years of age or older from Olmsted County, Minnesota, using TEE.[11] PFOs were present in 24.3 percent of subjects, and ASAs were present in 1.9 percent. During a mean follow-up period of 5.1 years, cerebrovascular events {transient ischemic attack (TIA), cerebral infarction, or death related to cerebral infarction} occurred in 41 patients. PFO was not a significant independent predictor of cerebrovascular events after adjustment for age and comorbid conditions (HR 1.46; 95% CI 0.74-2.88). Furthermore, there was no association between PFO size and risk of cerebrovascular events.

To summarize all the data, multiple case-control trials have found an association between cryptogenic stroke and the presence of PFO. However, population-based cohort studies have found no statistically significant association between the risk of first stroke and presence of PFO.

Treatment of Patent Foramen Ovale for Prevention of Recurrent Stroke

Treatment options vary and include medical options (antiplatelet agents or anticoagulants) and invasive methods (surgical treatment in the past and transcatheter device closure in recent years). The clinical course of a patient with a PFO who has a history of stroke or TIA and who does not receive treatment is unknown.

The goals of medical therapy are to prevent recurrence of an event once a sentinel event has already occurred or to prevent the initial occurrence of an event. Evaluation of the results of medical therapy is complicated for several reasons. First, the strength of the relationship between PFO occurrence and the central nervous system event must be established. If the central nervous system event is from another cause such as ascending aortic atheromatous debris, then medical therapy or surgical or percutaneous closure of the PFO will obviously be ineffective. Second, the specific anatomic pathology (e.g., the presence of PFO versus presence of ASA versus a combination) and the size of the PFO and shunt must be established at rest. The effectiveness of specific medical therapy (e.g., aspirin versus warfarin) must also be investigated.

The rationale for aspirin therapy comes from clinical data and from evidence suggesting that the paradoxical particles associated with transient ischemic events are small platelet/fibrin aggregates.[28] PFOs are treated with aspirin (300 mg/day) for secondary prevention of stroke or TIA among young patients after a single first event. At four years, aspirin therapy did not improve the frequency of recurrent cerebrovascular events in high-risk patients, such as those with septal abnormalities.[29] The efficacy of aspirin therapy is suggested by the French PFO-ASA study, which found that among 216 patients with a history of cryptogenic stroke who had a PFO alone, the incidence of recurrent stroke on aspirin therapy was only 2.3 percent after four years, a value comparable to the 4.2 percent risk seen in patients with neither PFOs nor ASAs.[29] Support for the use of aspirin also comes from the PICCS study, which did not demonstrate a statistically significant difference between the effects of aspirin and those of warfarin on the risk of subsequent stroke or death among patients with cryptogenic stroke and PFO.[26] However, PICSS was primarily designed as a prognostic study and was underpowered to demonstrate a treatment effect.

The American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy and the American Heart Association (AHA)/American Stroke Association Council on Stroke Practice Guidelines recommend antiplatelet therapy after the occurrence of cryptogenic stroke in the majority of patients. Warfarin therapy is suggested in the setting of known deep venous thrombosis or documented hypercoagulability (Table 1).[30][31]

Table 1. Summary of guidelines

Association	Recommendations
American College of Chest Physicians[28]	Antiplatelet therapy after cryptogenic stroke should include 1 of the following: (1) aspirin 50 to 325 mg daily; (2) aspirin 25 mg and extended-release dipyridamole 200 mg twice daily; or (3) clopidogrel 75 mg daily. Antiplatelet agents are recommended instead of oral anticoagulation unless a patient has a well-documented prothrombotic disorder. After cryptogenic ischemic stroke, in the presence of a PFO, antiplatelet therapy is recommended instead of warfarin unless a patient has evidence of deep venous thrombosis.
American Academy of Neurology[29]	After cryptogenic stroke, evidence indicates the risk of recurrent stroke or death does not vary between patients with and without PFOs who are treated medically. There is insufficient evidence to determine the superiority of antiplatelet agents vs. warfarin. There is insufficient evidence regarding the effectiveness of PFO closure.
AHA/American Stroke Association[30]	After noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events (class I, level of evidence A). Aspirin (50 to 325 mg/d), aspirin and extended-release dipyridamole in combination, and clopidogrel are all acceptable options for initial therapy (class IIa, level of evidence A). After ischemic stroke or TIA in patients with a PFO, antiplatelet therapy is reasonable to prevent a recurrent event (class IIa, level of evidence B). Warfarin is reasonable for high-risk patients who have other indications for oral anticoagulation, such as underlying hypercoagulable state or evidence of venous thrombosis (class IIa, level of evidence C). Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy (class IIb, level of evidence C).

AHA: American Heart Association, PFO: patent foramen ovales, TIA: transient ischemic attack

Despite medical therapy, up to 25% of patients with a history of cryptogenic stroke experience recurrent stroke or TIA within 4 years of the initial event.[25)28)] This has led a number of expert clinicians to conclude that mechanical closure should be the primary treatment modality for PFO patients after cryptogenic stroke. The treatment of symptomatic patients with PFOs who have failed medical therapy is either surgical or percutaneous closure with permanently implanted closure devices.

The reported efficacy of surgical closure in PFO patients with prior cerebrovascular ischemic events is variable,[32-35)] and randomized trials comparing medical therapy have not been performed. Surgical PFO closure consists of direct suture closure by open thoracotomy. In an age of excellent percutaneous PFO closure methods and results, surgical closure has become rare. The major inconvenience of this method is the invasive character and elevated complication rate.[33)]

The goals of PFO closure are to prevent neurologic events and to avoid the need for long-term anticoagulant therapy. Percutaneous transcatheter closure of a PFO is a catheter-based technique utilizing an atrial septal occlusion device.

A nonrandomized retrospective study directly compared 150 patients undergoing endovascular closure to 158 patients receiving medical therapy (79 oral anticoagulants and 79 antiplatelet agents). At four years, the incidence of death or recurrent events in patients undergoing defect closure (8.5%) was significantly lower than that seen in patients treated with aspirin (28.3%), but not significantly lower than that seen in patients treated with oral anticoagulation (13.3%).[36)] Defect closure was more effective than medical treatment in patients with complete closure and more than one cerebrovascular event at baseline. A systematic review based on the 10 studies of percutaneous PFO closure after a first embolic event in 1,355 patients and six studies of medical therapy in 895 patients showed: 1) The rate of recurrent neurologic events at one year was 0 to 4.9 percent with percutaneous closure and 3.8 to 12.0 percent with medical management; 2) Major complications associated with percutaneous closure occurred in 1.5 percent of patients; 3) Minor complications occurred in 7.9 percent.[37)] Because these studies were not randomized comparisons, definitive conclusions regarding the superiority of medical versus interventional management could not be reached from this analysis.

It has also been suggested that patients at high risk for recurrent events may benefit from defect closure after the first event.[38)] In prospective studies, only ASAs, increased shunt volume, and shunting at rest have been associated with increased recurrence risk.

There are no clear PFO therapy guidelines based on randomized trials. There are several ongoing randomized studies {Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial, Evaluation of the STARFlex Septal Closure System in Patients with a Stroke or TIA Due to the Possible Passage of Clot of Unknown Origin Through a Patent Foramen Ovale (CLOSURE-1), and Percutaneous closure (PC)-Trial: Patent Foramen Ovale and Cryptogenic Embolism}; their results may clarify the effectiveness of percutaneous closure as compared with medical therapy. Because prospective, randomized, controlled trials are not yet completed, there is no definite answer as to which therapy provides the best long-term prophylaxis against recurrent stroke. No prospective trial of percutaneous PFO closure among patients who have experienced cryptogenic stroke has been completed, and no device has been approved by the Food and Drug Administration (FDA) for PFO closure after cryptogenic stroke. Thus, the safety and effectiveness of devices for this indication are unknown. In 2007, the Food and Drug Administration Circulatory System Devices Panel agreed that randomized trials are absolutely necessary to determine the efficacy of percutaneous septal occluders in preventing recurrent cryptogenic stroke.[39)]

Patent Foramen Ovale Closure Devices

Although many other devices have been tested and used worldwide (Table 2), the most widely used PFO closure devices in the United States have been the Car-

Table 2. Examples of PFO closure devices

Device	Design
Amplatzer (AGA Medical Corp., Golden Valley, MN)	Self-centering double Nitinol discs connected by a waist; discs filled with Dacron; FDA approved for IDE use
CardioSEAL/STARFlex (NMT Medical, Boston, MA)	Noncentering double umbrella with a four-arm metallic framework covered in Dacron fabric; FDA approved for IDE use
Helex (W.L. Gore and Associates, Flagstaff, AZ)	Single-length Nitinol wire embedded into an expanded polytetrafluoroethylene patch
PFO-Star/Intrasept Occluder (Applied Biometrics Inc., Burnsville, MN)	Two Ivalon-square umbrellas expanded by four Nitinol arms
Premere (St. Jude Medical, St. Paul, MN)	Flexible polyester braided tether links a left atrial anchor to a right atrial disc covered in two layers of knitted polyester; long tunnel PFO device
Cierra (Cierra, Redwood City, CA)	Device welds together both sides of the PFO with a monopolar radiofrequency impulse under vacuum

PFO: patent foramen ovales, FDA: Food and Drug Administration, IDE: Investigational Device Exemption

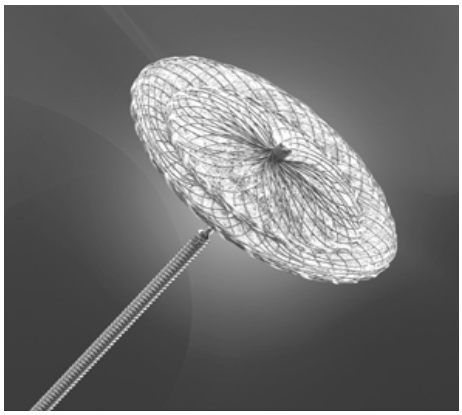

Fig. 2. Amplatzer PFO occluder. PFO: patent foramen ovale.

dioSEAL septal occluder device (NMT Medical, Boston, MA) and the Amplatzer PFO occluder device (AGA Medical, Golden Valley, MN). In the United States, both devices were recently withdrawn from humanitarian device exemption approval status, making them available for use exclusively in clinical research trials. Off-label use of other devices to close PFOs clearly occurs, but it has been impossible to accurately determine either the true extent of off-label use or the indications for which it occurs. Outside of the United States, and particularly in Europe, numerous devices have been approved and are being used for a variety of clinical indications.

The Amplatzer PFO occluder device is engineered as a self-expanding, double-disk device made from Nitinol wire tightly woven into two disks covered by Dacron patches that facilitate device endothelialization (Fig. 2). On the PFO occluder, the right atrial disk is larger (except on the 18-mm device, on which both disks are of the same size) than is the left atrial disk.[40] The Amplatzer device has many advocates who recognize its straightforward deliverability, retrievability, and utility in many PFO anatomical variants as some of its many positive attributes. Conversely, the overall rigidity, large amount of Nitinol used in its manufacturing, and occurrence of device erosion (albeit rare) remain noticeable shortcomings.[41]

The CardioSEAL occluder device consists of two square Dacron patches mounted among four spring arms made from a cobalt-based alloy, which are designed to enhance adherence to the interatrial septum (Fig. 3). A built-in spring-back mechanism allows the umbrella frame to resume its original shape after deformation during delivery.[42] Advocates of the CardioSEAL occluder device cite as its positive attributes its conformability and well-established use in large numbers of patients. By contrast, the device's propensity for surface thrombus formation and inability to redeploy following unsuccessful implantation remain major criticisms of the CardioSEAL device.[43]

Experimental devices under investigation include

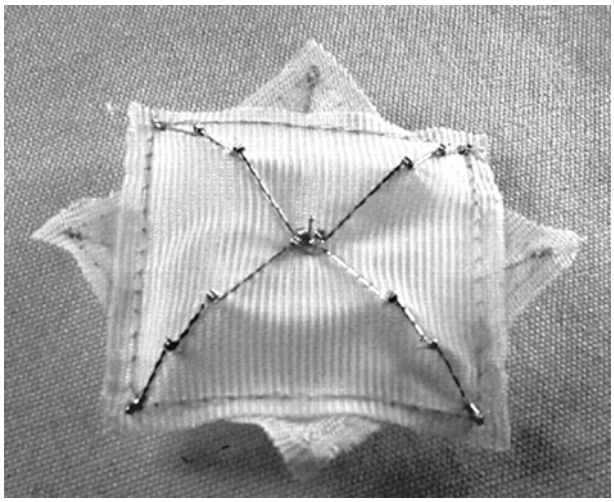

Fig. 3. CardioSEAL.

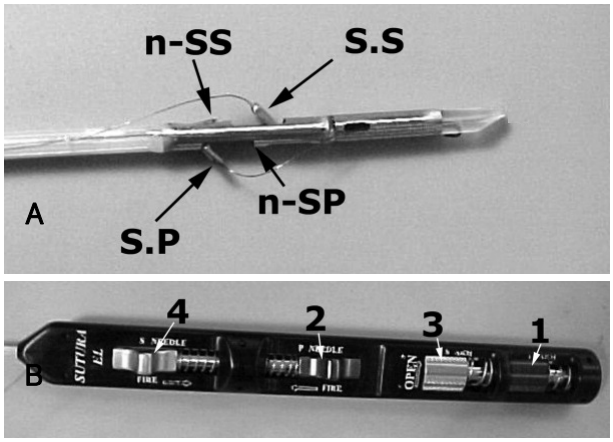

Fig. 4. HeartStitch suturing device. A: distal end of the HeartStitch catheter. S.P: the septum primum arm, n-SP: needle of the septum primum arm, S.S: septum secundum arm, n-SS: needle of the septum secundum arm. B: handle of the HeartStitch catheter. 1: control knob for opening the septum primum arm, 2: control for firing the septum primum needle, 3: control knob for the septum secundum arm, 4: control for firing the septum secundum needle.

HeartStitch (Sutura Inc., Fountain Valley, CA), which is based on SuperStitch technology (Fig. 4); the PFx™ closure system (Cierra, Redwood City, CA), which employs monopolar radiofrequency energy to effect closure of a PFO by welding the tissues of the septum primum and septum secundum together (Fig. 5); BioTREK™ (NMT Medical, Boston, MA), which is a totally bioabsorbable septal repair implant; and the Coherex FlatStent™ PFO closure system (Coherex Medical, Inc., Salt Lake City, UT), which is very lightweight and leaves minimal surface exposed in the LA (Fig. 6).[44]

Conclusion

PFOs are an important risk factor for TIA and stroke, 40% of which are "cryptogenic". The relationship between paradoxical (right-to-left) embolism through a

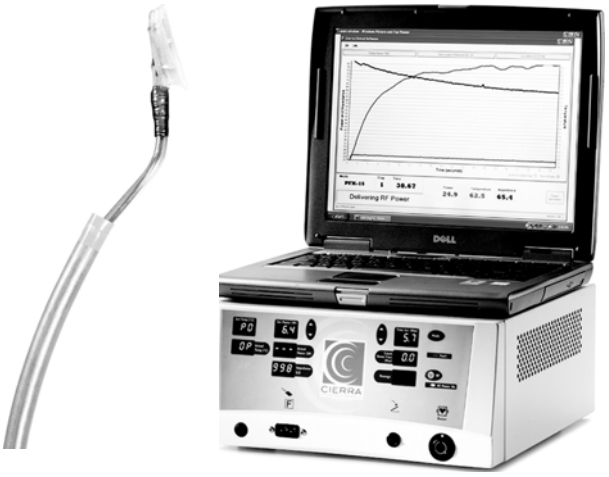

Fig. 5. PFx closure system.

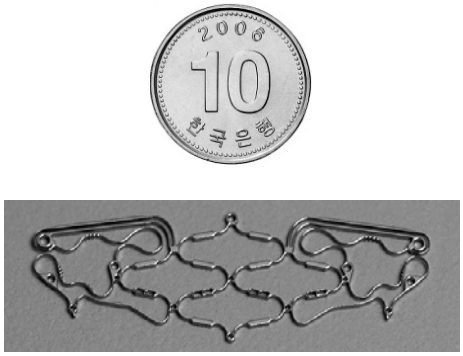

Fig. 6. Coherex.

PFO and stroke remains controversial. Conventional therapy for secondary prevention of recurrent stroke in patients with PFO includes medical therapy with antiplatelet agents or anticoagulants. The treatment of symptomatic patients with PFOs who have failed medical therapy is percutaneous closure with permanently implanted closure devices. Although the effect of percutaneous PFO closure has been superior to medical therapy in nonrandomized trials, the optimal therapy for patients with PFOs who have had cerebrovascular events is not well defined, because definitive randomized controlled trials have not been completed.

REFERENCES

1) Hausmann D, Mugge A, Becht I, Daniel WG. *Diagnosis of patent foramen ovale by transesophageal echocardiography and association with cerebral and peripheral emboli events. Am J Cardiol 1992;70:668-72.*
2) Ranoux D, Cohen A, Cabanes L, Amarenco P, Bousser MG, Mas JL. *Patent foramen ovale: is stroke due to paradoxical embolism? Stroke 1993;24:31-4.*
3) Schwerzmann M, Seiler C, Lipp E, et al. *Relation between directly detected patent foramen ovale and ischemic brain lesions in sport divers. Ann Intern Med 2001;134:21-4.*
4) Del Sette M, Angeli S, Leandri M, et al. *Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. Cerebrovasc Dis 1998;8:327-30.*
5) Hara H, Virmani R, Ladich E, et al. *Patent foramen ovale: current pathology, pathophysiology, and clinical status. J Am Coll Cardiol 2005;46:1768-76.*
6) Drighil A, El Mosalami H, Elbadaoui N, Chraibi S, Bennis A. *Patent foramen ovale: a new disease? Int J Cardiol 2007;122:1-9.*
7) Silver MD, Dorsey JS. *Aneurysms of the septum primum in adults. Arch Pathol Lab Med 1978;102:62-5.*
8) Agmon Y, Khandheria BK, Meissner I, et al. *Frequency of atrial septal aneurysms in patients with cerebral ischemic events. Circulation 1999;99:1942-4.*
9) Mugge A, Daniel WG, Angermann C, et al. *Atrial septal aneurysm in adult patients: a multicenter study using transthoracic and transesophageal echocardiography. Circulation 1995;91:2785-92.*
10) Schulz UG, Rothwell PM. *Differences in vascular risk factors between etiological subtypes of ischemic stroke: importance of population-based studies. Stroke 2003;34:2050-9.*
11) Meissner I, Khandheria BK, Heit JA, et al. *Patent foramen ovale: innocent or guilty?: evidence from a prospective population-based study. J Am Coll Cardiol 2006;47:440-5.*
12) Aberts GW, Comess KA, DeRook FA, et al. *Transesophageal echocardiographic findings in stroke subtypes. Stroke 1994;25:23-8.*
13) Jeanrenaud X, Bogousslavsky J, Payot M, Regli F, Kappenberger L. *Patent foramen ovale and cerebral infarct in young patients (French). Schweiz Med Wochenshr 1990;120:823-9.*
14) Oh BH, Park SW, Choi YJ, et al. *Prevalence of the patent foramen ovale in young patients with ischemic cerebrovascular disease: transesophageal contrast echocardiographic study. Korean Circ J 1993;23:217-22.*
15) Overall JR, Bone I, Lees KR. *Interatrial septal abnormalities and storke: a meta analysis of case control studies. Neurology 2000;55:1172-9.*
16) Berthet K, Lavergne T, Cohen A, et al. *Significant association of atrial vulnerability with atrial septal abnormalities in young patients with ischemic stroke of unknown cause. Stroke 2000;31:398-403.*
17) Caes FL, van Belleghem YV, Missoult LH, Coenye KE, van Nooten GJ. *Surgical treatment of impending paradoxical embolism through patent foramen ovale. Ann Thorac Surg 1995;59:1559-61.*
18) Chaturvedi S. *Coagulation abnormalities in adult with cryptogenic stroke and patent foramen oval. J Neurol Sci 1998;160:158-60.*
19) Cabanes L, Mas JL, Cohen A, et al. *Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. Stroke 1993;24:1865-73.*
20) Mattioli AV, Aquilina M, Oldani A, Longhini C, Mattioli G. *Atrial septal aneurysm as a cardioembolic source in adult patients with stroke and normal carotid arteries: a multicentre study. Eur Heart J 2001;22:261-8.*
21) 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.*
22) Webster MW, Chancellor AM, Smith HJ, et al. *Patent foramen ovale in young stroke patients. Lancet 1988;2:11-2.*
23) Lechat P, Mas JL, Lascault G, et al. *Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988;318:1148-52.*
24) 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;117:461-5.*
25) Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. *Patent foramen ovale and cryptogenic stroke in older patients. N Engl J Med 2007;357:2262-8.*
26) Homma S, Sacco RL, Di Tullio MR, et al. *Effect of medical treatment in stroke patients with patent foramen ovale. Circulation*

2002;105:2625-31.

27) Di Tullio MR, Sacco RL, Sciacca RR, Jin Z, Homma S. *Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. J Am Coll Cardiol 2007;49:797-802.*

28) Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. *Antithrombotic and thrombolytic therapy for ischemic stroke: the 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126 (3 Suppl):483S-512S.*

29) Mas JL, Arquizan C, lamy C, et al. *Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 2001;345:1740-6.*

30) Sacco RL, Adams R, Albers G, et al. *Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37:577-617.*

31) Messe SR, Silverman IE, Kizer JR, et al. *Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm. Neurology 2004;62:1042-50.*

32) Homma S, Di Tullio MR, Sacco RL, Sciacca RR, Smith C, Mohr JP. *Surgical closure of patent foramen ovale in cryptogenic stroke patients. Stroke 1997;28:2376-81.*

33) Dearani JA, Ugurlu BS, Danielson GK, et al. *Surgical patent foramen ovale closure for prevention of paradoxical embolism-related cerebrovascular ischemic events. Circulation 1999;100 (19 Suppl):II171-5.*

34) Devuyst G, Bogousslavsky J, Ruchat P, et al. *Prognosis after stroke followed by surgical closure of patent foramen ovale: a prospective follow-up study with brain MRI and simultaneous transesophageal and transcranial Doppler ultrasound. Neurology 1996;47:1162-6.*

35) Ruchat P, Bogousslavsky J, Hurni M, Fischer AP, Jeanrenaud X, von Segesser LK. *Systematic surgical closure of patent foramen ovale in selected patients with cerebrovascular events due to paradoxical embolism: early results of a preliminary study. Eur J Cardiothorac Surg 1997;11:824-7.*

36) Windecker S, Wahl A, Nedeltchev K, 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.*

37) 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.*

38) Wu LA, Malouf JF, Dearani JA, et al. *Patent foramen ovale in cryptogenic stroke: current understanding and management options. Arch Intern Med 2004;164:950-6.*

39) Slottow TL, Steinberg DH, Waksman R. *Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel meeting on patent foramen ovale closure devices. Circulation 2007;116:677-82.*

40) Meier B. *Closure of patent foramen ovale: technique, pitfalls, complications, and follow up. Heart 2005;91:444-8.*

41) Trepels T, Zeplin H, Sievert H, et al. *Cardiac perforation following transcatheter PFO closure. Catheter Cardiovasc Interv 2003;58:111-3.*

42) Gupta A, Kapoor G, Dalvi B. *Transcatheter closure of atrial septal defects. Expert Rev Cardiovasc Ther 2004;2:713-9.*

43) Anzai H, Child J, Natterson B, et al. *Incidence of thrombus formation on the CardioSEAL and the Amplatzer interatrial closure devices. Am J Cardiol 2004;93:426-31.*

44) Majunke N, Sievert H. *ASD/PFO devices: what is in the pipeline? J Interv Cardiol 2007;20:517-23.*