PFO and Stroke: The Hidden Connection

If the results of clinical trials support the more widespread use of PFO closure, the national demand for this procedure will be potentially explosive.

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This article was originally published in the September 2003 issue of Endovascular Today. *It is reprinted here in its entirety.*

Stroke is the leading cause of disability and the third leading cause of death in the US. Identifying the causes of neurologic ischemic syndromes is essential to any strategy intended to prevent the catastrophic consequences of cerebral infarction. Figure 1 is a classification scheme depicting that stroke may be ischemic or hemorrhagic at its onset and further diagrams multiple underlying etiologies of the ischemic variety, which collectively represent approximately 85% of all strokes. When such classification methods are applied to large populations of stroke patients, however, the largest single category is usually stroke of unknown cause, more generally labeled as cryptogenic stroke. Although commonly recognized causes such as carotid artery stenosis and atrial fibrillation each generally account for 20% to 25% of stroke etiologies in most series, cryptogenic stroke remains the "diagnosis" in approximately 40% of patients.[1,2]

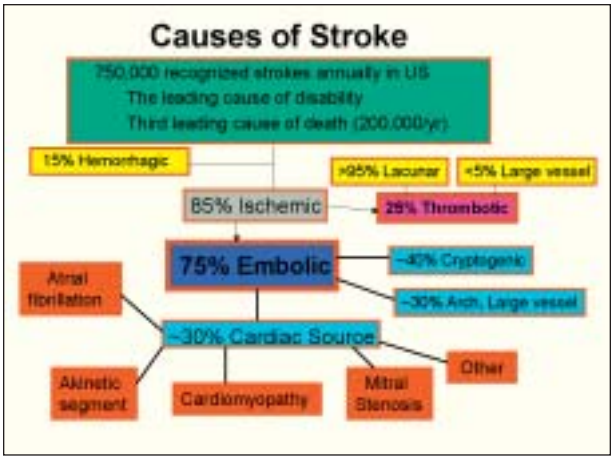

Figure 1. The causes of stroke.

Since the initial reports of unexpectedly high prevalence of patent foramen ovale (PFO) in younger patients with cryptogenic stroke appeared in 1988,[3,4] there has been growing interest and experience in diagnosing and treating these patients both medically and with surgical or percutaneous closure. The potential to eliminate paradoxical embolism via PFO as a mechanism for stroke has excited the passions of both the advocates of such an approach as well as the skeptics. This article attempts to review the background of PFO as a potential enabler of stroke, diagnosis of PFO, the results of medical management and defect closure, the potential relationship of PFO to other important clinical problems, and the current and future status of percutaneous defect closure.

BACKGROUND

Organogenesis is largely complete by the end of the first trimester, at which time the fetal heart is not much larger than a grape. During the early stages of cardiac formation, the cardiac tube folds upon itself, and additional folds, growths, resorptions, and tissue specialization result in valve formation and septation of the heart. During this period, the developing central nervous system has the highest oxygen requirements, and blood flow pathways through the heart evolve in such a way as to ensure that relatively highly oxygenated blood returning from the placenta is preferentially diverted to the central nervous system. Patency of the foramen ovale specifically accomplishes this goal by allowing this blood to cross from the inferior vena cava through the foramen, into the left heart and aorta, from which it travels to the central nervous system via arteries arising from the arch. Meanwhile, the less oxygen-rich blood returning via

the superior vena cava courses through the right heart to the pulmonary artery, through the ductus arteriosus, and into the descending thoracic aorta, nutrifying tissues in need of less oxygen.

The atrial septum forms in stages. The septum primum originates from a superior fold in the cardiac tube and grows toward nubbins of endocardial cushions, eventually to fuse with them by closing the ostium primum. Around this time, septum primum tissue near its superior and posterior origination point begins to resorb, creating the ostium secundum. A thick arc of tissue begins to develop at the posterior, superior aspect of the right atrium and grows anteriorly and inferiorly to cover the ostium secundum. This leaves a pathway through the septum between the delicate and more inferior primum and the thicker and more superior secundum, with the entrance directed toward the inferior vena cava and the exit into the left atrium at the superior edge of the septum primum. The foramen ovale is therefore a pathway between two sheets of tissue, similar to the space between drawn curtains, rather than a hole.

After birth, blood flow through the lungs increases abruptly to equal systemic circulation. Left atrial inflow and pressure rise, and the septum primum is passively closed against the septum secundum. Approximately 75% of septa fuse shortly after birth. The remaining 25% do not fuse, resulting in patency of the foramen, thereby making PFO more common than left-handedness or red hair. In autopsy series,[5] such PFOs are described as "probe-patent," meaning that a 1-mm to 3-mm probe can be passed snugly through the pathway from the right to the left atrium. In patients with cryptogenic stroke undergoing closure of the PFO, the defect is generally substantially different than this normal variant in several ways. Most importantly, it is larger. In most reported series, the balloon-stretched diameter ranges between 5 mm and 24 mm (average, 12.5 mm). Second, the septum primum tissue is often (20%-25% of patients) highly redundant and floppy, passing more than a centimeter beyond the septal plane in both directions, to which the term *atrial septal aneurysm* (ASA) is widely applied. The coexistence of PFO and ASA results in a two- to fourfold increase in the risk of recurrent events in patients with cryptogenic stroke as compared to patients with PFO alone.[6-9] Third, the primum tissue may be grossly defective and contain multiple fenestrations, giving the septum a "Swiss-cheese" appearance.

In 1988, Webster et al[3] and Lechat et al[4] separately reported that the prevalence of PFO in relatively young cryptogenic stroke patients was much higher than the 10% to 30% prevalence previously reported in population and autopsy series, raising the possibility that paradoxical embolism via PFO might be an important cause of stroke when other commonly recognized causes are absent. Arguments against such a mechanism include the failure to identify deep vein thrombosis in the overwhelming majority (>95%) of cryptogenic stroke patients in whom it is sought, the high prevalence of PFO in the general population, and the failure to document actual passage of thrombus through the defect, although isolated case reports of bulky thrombus trapped in the foramen exist.[10,11]

Arguments supporting paradoxical embolism as an etiology of stroke include the finding of small (<4 mm) cerebral emboli in 85% of patients undergoing angiography within the first 12 hours after stroke onset;[12] the relation of right-to-left shunt capacity with risk of recurrent stroke;[13-15] and the accumulating evidence that defect closure results in much lower rates of recurrent stroke than other management strategies. The observation that deep vein thrombosis is almost never found in these patients is countered by the fact that there is no noninvasive imaging modality that can detect venous thrombi in the size range of the emboli seen on cerebral angiography. Notwithstanding this phenomenon, there are multiple reports of stroke shortly after pulmonary embolism in patients with PFO and deep vein thrombosis.

DIAGNOSING PFO

PFO is a diagnosis that cannot be made unless it is specifically sought.[16-21] It cannot be detected on physical examination, chest x-ray, electrocardiography, or conventional echocardiography. Definite evidence of PFO can be made by direct inspection during open heart surgery or by passing a catheter through the defect, but these are obviously impractical as diagnostic methodologies. Currently, the gold standard noninvasive method for diagnosing PFO is transesophageal echocardiography (TEE) performed during intravenous injection of agitated saline as a contrast agent, usually accompanied by provocative maneuvers including Valsalva and cough.

Such imaging demonstrates dense opacification of the right atrium and the subsequent appearance of bubbles in the left atrium. Such left-sided opacification can be continuous, intermittent with inspiration, or only in conjunction with one or more of these provocative maneuvers. Color-flow Doppler interrogation is far too insensitive and, given the surrounding flow patterns from superior vena cava and pulmonary venous inflow, is too nonspecific to offer much additional utility. However, identification of a fenestration in the septum primum or of an atrial septal defect, both of which are characterized by essentially continuous left-to-right flow, can supplement or fundamentally alter the diagnosis, respectively. Additionally, TEE establishes the presence or absence of ASA and allows examination of the left atrial appendage for alternative/additional sources of thromboemboli.

The principal drawback of TEE is that patients are usually moderately to heavily sedated for the procedure, and this sedation often interferes with performance of effective cough or Valsalva strain. Especially with second harmonic imaging, false-positive appearance of contrast material in the left atrium may occur in 5% to 8% of patients due to transpulmonary transport, usually identifiable by virtue of the very small size of the bubbles (resembling rouleaux) and the delayed appearance in the left heart by 3 seconds to 5 seconds after appearance in the right atrium. Transthoracic echocardiography with intravenous injection of agitated saline contrast obviously requires no sedation and is a highly specific testing modality when positive for the appearance in the left heart, but it suffers from limited sensitivity. It is, therefore, a reasonable and simple screening tool, but it is insufficient to rule out the presence of a PFO if it is negative. Transcranial Doppler (TCD) with intravenous agitated saline injection is potentially a very useful screening tool that depicts the appearance of reflective bubbles in the intracranial circulation and does not require sedation. Provocative measures can be employed, and the timing of the appearance of contrast after such maneuvers may help to distinguish between intracardiac and extracardiac (eg, pulmonary arteriovenous fistula) shunts. The reported accuracy of TCD as compared with TEE is in the range of 90% and may improve with refinements in technology, such as power TCD, which enables gated imaging.

MEDICAL MANAGEMENT

There has not been a randomized clinical trial comparing medical (antithrombotic) therapy with any other form of treatment in patients with stroke due to presumed paradoxical embolism via PFO. The standard of care for the management of such patients has been treatment with antiplatelet and/or anticoagulant medication, but there is no evidence to suggest that such treatment is more (or less) effective than no treatment at all. In the 1990s, a number of authors reported recurrent stroke rates in patient populations in whom such treatment was empirically chosen.[12,22] These reports shared as the principal flaw the nonrandomized nature of treatment assignments, and some patients believed to be at highest risk for recurrent events (on the basis of large shunts and/or the presence of ASA and/or the presence of multiple infarctions on brain imaging) were assigned to surgical closure. From these series, the risk of recurrent stroke ranged from 1.2% to 31% (average, 3%-8%).

Among patients with associated ASA, the risk was usually two- to four-fold higher than in patients without this variant. In the WARRS study,[23] 2,206 patients with previous "noncardioembolic" stroke (absence of atrial fibrillation, akinetic segment, and carotid stenosis scheduled for surgical treatment) were randomized to treatment with aspirin or warfarin, with the primary endpoint being the composite of death or recurrent stroke at 2 years. There was no placebo group. The two treatments were associated with statistically similar outcomes: primary endpoint reached in 16% of patients treated with aspirin versus 17.8% of anticoagulated patients, and the risk of bleeding was higher in the latter group. Death accounted for 27% of the endpoints, and only 26% of the previous strokes were cryptogenic. The PICSS study[24] was a substudy of 630 patients in the WARRS trial who underwent TEE. The same endpoints as in WARRS were assessed and correlated with septal anatomy. Most (58%) of the patients, however, did not have cryptogenic stroke, and most (66%) did not have PFO. Death accounted for 23% of the endpoints. PFO was more common and large PFO (as measured with calipers on the TEE) was much more common in patients with cryptogenic versus known subtype strokes. Traditionally recognized stroke risk factors were significantly more prevalent among patients with noncryptogenic stroke. Endpoints occurred at statistically similar rates in the aspirin and warfarin treatment groups.

The lowest reported rates of recurrent stroke were reported by Mas et al[8] in a group of 581 patients with cryptogenic stroke. The patient population ranged in age from 18 to 55 years; all patients underwent contrast TEE, were treated with aspirin, and were followed for a mean of 37 months. Outcomes were correlated with septal anatomy characterized as normal, PFO only, ASA only, or PFO and ASA. The derived 4-year recurrence rates for ischemic neurologic events were: none for ASA alone, 2.3% for PFO alone, and 4.2% among patients with normal septal anatomy. These strange results are explained by the fact that conventional stroke risk factors were much more prevalent among patients with normal septal anatomy. Among patients with both PFO and ASA, the rate was a staggeringly higher (15.2%). This series represents the most rigorously, prospectively studied group of its kind and conclusively confirms the synergistic risk associated with this combination of defects.

DEFECT CLOSURE

Surgical closure was employed in the management of patients generally considered to be at high risk for medical therapy before the more widespread adoption of percutaneous closure. Several series of such patients have been reported, and the recurrence rates for stroke have generally ranged from 0% to 1.1%.[25-28] One series of 30 patients included follow-up assessment of residual shunt that was detected in four (13.2%) of the group, although there were no recurrent events.[26] The introduction and development of percutaneous device closure of PFO has resulted in a growing number of reports[29-32] regarding the safety and efficacy of the procedure. Reasons to favor this approach to

defect closure over surgery are multiple and include the obvious advantages of being less invasive, associated with a much shorter hospital stay, avoiding major surgery in patients with false-positive contrast TEE or in patients with a different location of right-to-left shunt (pulmonary A-V fistula), and lower cost.

The technique has evolved to the point that it can be performed under mild conscious sedation in less than 30 minutes. The advent of intracardiac echocardiography[33,34] has made intraprocedural TEE unnecessary and similarly assists in ensuring complete defect closure, including the identification of coexistent fenestrations of the septum primum or intrapulmonary shunts, which can also be obliterated percutaneously. These reports share a number of findings: percutaneous closure is safe and feasible; defect diameters generally range from 5 mm to 24 mm (average, 12-13 mm); the residual leak rate is approximately 20% at the end of the implant procedure and decreases to approximately 5% at 6 months. Successful device deployment is achieved in 98% to 100% of patients. Infection is rare, as is device embolization, which is mostly associated with a separable device. Thrombus formation on the device has been rare, but has occasionally been responsible for recurrent neurologic events and has necessitated surgical explantation.

Atrial arrhythmias have occurred in approximately 5% of patients within the first few weeks after implantation. Almost every reported series has shown annualized recurrent stroke rates of less than 1.6%. In the largest analyzed series from Sievert et al (personal communication updating previous published observations),[35] more than 500 patients were studied before and after PFO device closure to assess the annual risk of recurrent ischemic neurologic events (stroke plus TIA) after an index stroke. Before closure, the recurrence rate was 26% annually; afterward it was only 2.5%.

POTENTIAL RELATIONSHIP BETWEEN PFO AND OTHER CLINICAL PROBLEMS

In some of the earliest reports relating to stroke and PFO, patient demographics showed an unexpectedly high prevalence of migraine headache. Since then, migraine has been quite common among patients referred for percutaneous closure of PFO for other reasons. In my own experience in more than 250 patients, approximately 70% have a history of migraine. Several authors[36,37] have reported a marked improvement in migraine frequency and/or intensity after PFO closure, especially among patients whose headaches are preceded by aura. The cause of migraine headache is unknown, but these observations suggest that the mechanism, at least in some patients, may be shunting of a vasoactive agent through a PFO, an agent that would otherwise be inactivated during transpulmonary circulation.

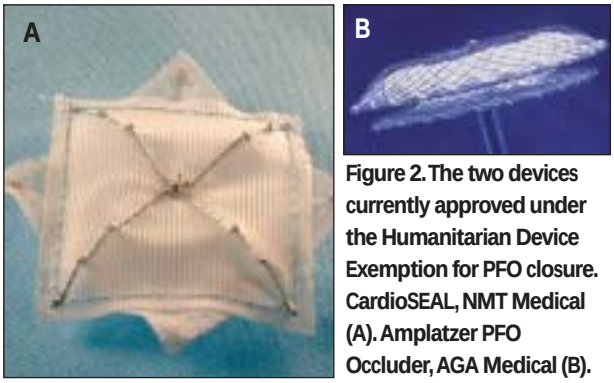

Figure 2. The two devices currently approved under the Humanitarian Device Exemption for PFO closure. CardioSEAL, NMT Medical (A). Amplatzer PFO Occluder, AGA Medical (B).

In addition to paradoxical embolism enabled by a right-to-left shunt through a PFO, such shunting, if of sufficient magnitude, may result in oxygen-resistant systemic arterial desaturation. This phenomenon has been observed in cases of acute or chronic right atrial hypertension or tricuspid regurgitation directed at the fossa ovalis. Clinical settings in which these circumstances arise include acute pulmonary embolism,[38,39] right ventricular infarction, chronic obstructive lung disease, and recent cardiac or lung surgery. There is a growing base of literature concerning decompression sickness in divers[40-42] who have not violated safety guidelines, among whom there is a high prevalence of PFO. Some divers have resumed this activity after percutaneous closure of the defect.

Finally, although cerebral infarction is generally the most disabling consequence of paradoxical embolism via PFO, other ischemic problems can be caused by this mechanism, including TIA, transient global amnesia, myocardial infarction, and systemic thromboembolism. When these events are judged to be attributable to PFO, their prognostic implications are probably similar to those of an index or recurrent cryptogenic stroke.

CURRENT AND FUTURE STATUS OF PERCUTANEOUS PFO CLOSURE

At present in the US, two devices have been approved under the Humanitarian Device Exemption for catheter-based PFO closure (CardioSEAL, NMT Medical, Inc., Boston, MA; Amplatzer PFO Occluder, AGA Medical Corporation, Golden Valley, MN)(Figure 2). Under the Humanitarian Device Exemption, the maximum number of patients to be treated is anticipated to be less than 4,000 annually for each device. For a hospital to purchase these devices, there must be a certified implanter on the medical staff and the hospital's Institutional Review Board must approve the performance of such closure procedures at the hospital. The FDA-approved labeled indication for use in patients with PFO requires that patients to be treated will have sustained a second stroke presumably due to paradoxical embolism via a

PFO, and that this event must have occurred while on "conventional medical therapy," which is further defined as therapeutic anticoagulation.

There are approximately 750,000 recognized strokes in the US annually. In approximately 300,000 (40%) of these patients, the strokes are characterized as cryptogenic. This is most likely (but not exclusively) true of patients under the age of 55 years, in whom conventional stroke risk factors such as diabetes, carotid disease, atrial fibrillation, myocardial infarction, and hypertension are less prevalent. Previous studies suggest that the prevalence of PFO among these patients is in the range of 50% to 70%, raising the possibility that as many as 150,000 to 210,000 patients per year may suffer a stroke due to paradoxical embolism. This number is exclusive of patients with other diagnoses that might be related to PFO and who conceivably could benefit from defect closure, such as patients with TIA, migraine, arterial desaturation, decompression sickness, and other systemic embolic diagnoses.

The regulatory status of these closure devices is unlikely to change until a compelling case for the superiority of PFO closure over medical therapy can be demonstrated by prospective, randomized clinical trials. Such trials are just getting underway. At the present time, neurologists and other stroke care providers should be encouraged to screen patients with cryptogenic stroke for PFO and to refer them to centers involved in these trials. High-volume centers with skilled specialists will likely develop across the country. If the results of clinical trials support the more widespread use of PFO closure in the routine management of these patients, the national demand for this procedure will be potentially explosive. It will be important for recognized centers of excellence to participate in the training of interventional physicians in the safe and effective performance of these procedures so that the demand can be met. ■

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1. Sacco RL, Ellenberg JH, Mohr JP, et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. *Ann Neurol.* 1989;25:382-390.
2. Sherman DG. Prevention of cardioembolic stroke. In: Norris JW, Hachinski VC, eds. Prevention of Stroke. New York, NY: Springer Verlag; 1991:149-159.
3. Lechat P, Mas J-L, Lacault G, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med.* 1988;318:1148-1152.
4. Webster MW, Chacellor AM, Smith HJ, et al. Patent foramen ovale in young stroke patients. *Lancet.* 1988;2:11-12.
5. 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.
6. DeCastro S, Cartoni D, Fiorelli M, et al. Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke.* 2000;31:2407-2413.
7. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke. A meta-analysis of case-control studies. *Neurology.* 2000;55:1172-1179.
8. Mas J-L, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septum aneurysm, or both. *N Engl J Med.* 2001;345:1740-1746.
9. Cabanes L, Mas J-L, 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: a study using transesophageal echocardiography. *Stroke.* 1993;24:1865-1873.
10. Johnson BI. Paradoxical embolism. *J Clin Pathol.* 1951;4:316-332.
11. Mas J-L. Patent foramen ovale, stroke and paradoxical embolism. *Cerebrovasc Dis.* 1991;1:181-183.
12. Bogousslavsky J, Garazi S, Jeanrenaud X, et al. Stroke recurrence in patients with patent foramen ovale: the Lausanne study. *Neurology.* 1996;46:1301-1305.
13. Homma S, DiTullio MR, Sacco RL, et al. Characteristics of patent foramen ovale associated with cryptogenic stroke: a biplane transesophageal echocardiographic study. *Stroke.* 1994;25:582-586.
14. Hausman D, Mugge A, Daniel WG. Identification of patent foramen ovale permitting paradoxic embolism. *J Am Coll Cardiol.* 1995;26:1030-1038.
15. Schuchlenz HW, Weihs W, Horner S, et al. The association between the diameter of a patent foramen ovale and the risk of embolic cerebrovascular events. *Am J Med.* 2000;109:456-462.
16. Albert A, Mueller HR, Hetzel A. Optimized transcranial Doppler technique for the diagnosis of cardiac right-to-left shunts. *J Neuroimaging.* 1997;7:159-163.
17. Anzola GP, Renaldini E, Magoni M, et al. Validation of transcranial Doppler sonography in the assessment of patent foramen ovale. *Cerebrovasc Dis.* 1995;5:194-198.
18. Autore C, Cartoni D, Piccininno M. Multiplane transesophageal echocardiography and stroke. *Am J Cardiol.* 1998;82(12A):79G-81G.
19. Belkin RN, Pollack BD, Ruggiero ML, et al. Comparison of transesophageal and transthoracic echocardiography with contrast and color flow Doppler in the detection of patent foramen ovale. *Am Heart J.* 1994;128:520-525.
20. Devuyst G, Despland PA, Bogousslavsky J, et al. Complementarity of contrast transcranial Doppler and contrast transesophageal echocardiography for the detection of patent foramen ovale in stroke patients. *Eur Neurol.* 1997;38:21-25.
21. DiTullio M, Sacco RL, Venketasubramanian N, et al. Comparison of diagnostic techniques for the detection of a patent foramen ovale in stroke patients. *Stroke.* 1993;24:1020-1024.
22. Mas J-L, Zuber M. Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. *Am Heart J.* 1995;130:1083-1088.
23. Mohr JP, Thompson JLP, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med.* 2001;345:1444-1451.
24. Homma S, Sacco RL, DiTullio MR, et al. Effect of medical treatment in stroke patients with patent foramen ovale. Patent Foramen Ovale in Cryptogenic Stroke Study. *Circulation.* 2002;105:2625-2631.
25. Guffi M. Bogousslavsky J, Jeanrenaud X, et al. Surgical prophylaxis of recurrent stroke in patients with patent foramen ovale: a pilot study. *J Thorac Cardiovasc Surg.* 1996;112:260-263.
26. 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;47:1162-1166.
27. 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(suppl II):II171-II175.
28. Ruchat P, Bogousslavsky J, Hurni M, et al. 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;11:824-827.
29. Hung J, Landzberg MJ, Jenkins KJ, et al. Closure of patent foramen ovale for paradoxical emboli: intermediate-term risk of recurrent neurological events following transcatheter device placement. *J Am Coll Cardiol.* 2000;35:1311-1316.
30. Windecker S, Wahl A, Chatterjee T, et al. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. *Circulation.* 2000;101:893-898.
31. Martin F, Sanchez PL, Doherty E, et al. Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Circulation.* 2002;106:1121-1126.
32. Sommer RJ, Kramer PH, Sorenson SG, et al. Closure of patent foramen ovale with the CardioSEAL septal occluder: infrequent recurrent Thrombotic neurologic events. *Am J Cardiol.* 2002;90(suppl 6A):136H.
33. Zanchetta M, Rigatelli G, Onorato E. Intracardiac echocardiography and transcranial Doppler ultrasound to guide closure of patent foramen ovale. *J Invas Cardiol.* 2003;15:93-96.
34. Bartel T, Konorza T, Arjumand J, et al. Intracardiac echocardiography is superior to conventional monitoring for guiding device closure of interatrial communications. *Circulation.* 2003;107:795-797.
35. Sievert H, Ostermayer S, Billinger K, et al. Transcatheter closure of patent foramen ovale for prevention of paradoxical embolism and recurrent embolic stroke with the CardioSEAL STARFlex occluder. *Am J Cardiol.* 2002;90(suppl 6A):38H.
36. Wilmshurst PT, Nightingale S, Walsh KP, et al. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. *Lancet.* 2000;356:1648-1651.
37. Milhaud D, Bogousslavsky J, van Melle G, et al. Ischemic stroke and active migraine. *Neurology.* 2001;57:1805-1811.
38. Konstantinides S, Geibel A, Kasper W, et al. Patent foramen ovale is an important predictor of adverse outcome in patients with major pulmonary embolism. *Circulation.* 1998;97:1946-1951.
39. Donti A, Giardini A, Formigari R, et al. Treatment of recurrent stroke and pulmonary thromboembolism with percutaneous closure of a patent foramen ovale and placement of inferior vena cava filter. *Cathet Cardiovasc Intervent.* 2003;58:413-415.
40. Saary MJ, Gray GW. A review of the relationship between patent foramen ovale and type II decompression sickness. *Aviat Space Environ Med.* 2001;72:1113-1120.
41. Bove AA. Risk of decompression sickness with patent foramen ovale. *Undersea Hyperb Med.* 1998;25:175-178.
42. Knauth M, Ries S, Pohimann S, et al. Cohort study of multiple brain lesions in sport divers: role of a patent foramen ovale. *Br Med J.* 1997;314:701-705.