Interatrial Communications, Stroke, and Migraine Headache

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This review will familiarize physicians with the embryology, types, and incidence of various interatrial communications; summarize and highlight the potential association of interatrial communications with stroke, platypnea-orthodeoxia syndrome, neurologic decompression sickness in divers, and migraine headaches; discuss various therapeutic modalities available for closure of interatrial communications; and outline future directions in this rapidly evolving field.

Interatrial shunts, particularly patent foramen ovale (PFO) and atrial septal defect (ASD), are present in about one quarter of the population and cause right-to-left shunting when the right atrial pressure exceeds that of the left.1-3 Although the presence of a PFO generally had been regarded as having minimal clinical significance,4 PFO has been implicated in several medical conditions, including cryptogenic stroke secondary to paradoxical embolism,5-9 migraine headache,10-16 platypnea-orthodeoxia syndrome,17-18 and neurologic decompression illness in scuba divers.19-21 Percutaneous closure of interatrial communications can now be achieved and has been associated with very high success rates and minimal complication rates.13,22-27 This procedure may become an effective treatment for platypnea-orthodeoxia syndrome and for neurologic decompression sickness in scuba divers. It also may serve as a secondary prevention of cryptogenic stroke and may prove more effective than any previous therapy for migraine headache. This review will familiarize physicians with the embryology, types, and incidence of various interatrial communications; summarize and highlight the potential association of interatrial communications with stroke, platypnea-orthodeoxia syndrome, neurologic decompression sickness in divers, and migraine headaches; discuss various therapeutic modalities available for closure of interatrial communications; and outline future directions in this rapidly evolving field.

EMBRYOLOGY AND ANATOMY
The formation of the interatrial septum begins in the fifth week of gestation. The septum primum grows caudally from the superior portion of the common atrium and fuses with the endocardial cushions. This results in closure of a defect known as the ostium primum. Another defect, the ostium secundum, forms from the partial resorption of the septum primum.
A second septum--the septum secundum--arises on the right side of the septum primum in the superior right atrium and grows caudally to cover the ostium secundum. The ostium secundum is not covered completely because of the presence of the foramen ovale.
The foramen ovale consists of the septum primum and septum secundum, which are joined parallel to a slitlike valve. This valve allows oxygenated venous blood to bypass the pulmonary circulation and directly enter the systemic arterial circulation of the fetus during gestation.28,29 In gestation, oxygenated blood from the umbilical vein enters the right atrium from the inferior vena cava. Because right atrial pressure exceeds that of the left due to high pulmonary vascular resistance, blood is shunted directly through the foramen ovale to the left atrium and into the systemic circulation. Postpartum, after the lungs expand, the left atrial pressure exceeds that of the right, causing the septum primum to press against the septum secundum. Thus, right-to-left shunting ceases. In most persons, the septum primum and the septum secundum fuse during the first year of life and the foramen ovale is closed. Lack of postnatal closure results in a PFO (Figure 1). The foramen ovale remains patent in about a quarter of adults.2,3,30 The incidence of PFO is inversely related to age, suggesting that over time, the PFO closes spontaneously in some patients. In one study,3 the prevalence of PFO progressively declined with increasing age, from 34.3% during the first 3 decades of life to 25.4% during the 4th through 8th decades, and to 20.2% during the 9th and 10th decades. However, older patients tend to have larger PFOs than younger patients.
ASD is the third most common congenitally acquired cardiac disorder (after bicuspid aortic valve and ventricular septal defects): it occurs in 0.1% of all births and accounts for up to 30% of all adult congenital heart lesions.31 Although the usual direction of shunting is left to right in patients with
either a PFO or ASD, interatrial right-to-left shunting occurs in both conditions when the right atrial pressure exceeds that of the left, such as during the Valsalva maneuver or coughing. The 3 types of ASDs are primum ASD, secundum ASD, and sinus venosus ASD. A primum ASD develops if the septicum primum does not fuse with the endocardial cushions and accounts for 15% of all ASDs. A secundum ASD results if the fossa ovalis is not completely covered by the septum secundum either because of excessive resorption of the septum primum or because of inadequate growth of the septum secundum. Secundum ASDs account for 75% of all ASDs, which makes them the most common ASD. They are typically isolated defects and may not be detected in many patients until adulthood. Sinus venosus ASDs, which account for 5% to 10% of all ASDs, are associated with abnormal insertion of the superior or inferior vena cava. The insertion site overrides the interatrial septum with an interatrial communication occurring at the mouth of the corresponding vein. Mutations of the myosin gene have been linked to inheritance of ASDs, and it appears that both PFOs and ASDs are inherited in an autosomal dominant pattern.

**DETECTION OF INTERATRIAL COMMUNICATIONS**

Detection of interatrial communications can be accomplished by several imaging modalities. These include transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and transcranial Doppler ultrasonography (TCD) with microbubble injection. Although TTE with echocontrast injection is easy to perform and relatively inexpensive, it has poor sensitivity for detection of interatrial communications compared with TEE and TCD. TEE is an excellent modality for visualization of the interatrial septum and interatrial communications. When used with microbubble echocontrast injection, it can reliably exclude the presence of an interatrial communication. It also can provide important anatomic information about associated conditions, such as atrial septal aneurysm (ASA). Finally, TEE can provide excellent information about cardiac structure and function, including other causes of cardiac embolization, such as atrial appendage thrombus, left ventricular thrombus, valvular vegetation/endocarditis, and intracardiac tumors. However, TEE is an invasive and more expensive approach and may be associated with moderate patient discomfort.

TCD is a simple and noninvasive method for detection of right-to-left shunting. Multiple studies have demonstrated that it is at least as sensitive in detecting intracardiac shunts as TEE. However, TCD does not provide any information about which type of intracardiac shunting is present or about cardiac structure or function, including other possible cardiac sources of embolization. Finally, all positive TCD studies need to be followed up by a transesophageal or intracardiac echocardiogram to define the cause of the right-to-left shunting and to exclude pulmonary arterial-venous shunting.

**CRYPTOGENIC STROKE AND INTERATRIAL COMMUNICATIONS**

A cryptogenic stroke is defined as a stroke of unknown cause. By definition, it is a diagnosis of exclusion. Two recent large observational studies reported that 40% of stroke cases occurring in patients younger than 55 years were classified as cryptogenic. Many cases of cryptogenic stroke have been attributed to paradoxical embolism—a clot that originates in the venous system and reaches the arterial circulation by right-to-left shunting through a central communication. It has been estimated that up to 70,000 of the 750,000 annual strokes in the United States may be attributed to paradoxical embolism through a PFO.

Although a causal relationship has not been firmly established, the prevalence of interatrial communications appears to be increased in patients who have had a cryptogenic stroke. According to some reports, the association between stroke and interatrial communications is stronger among patients with a PFO and an ASA than it is among patients with a PFO alone. Other reports dispute this finding. A substudy of the PFO in Cryptogenic Stroke Study (PICSS), which included 630 patients with cryptogenic stroke who had undergone TEE, seems to contradict these data. In this study, patients who had an ASA and a PFO were not at increased risk for stroke compared with patients who only had a PFO. The source of emboli in the majority of cases is thought to be small venous clots that cross the interatrial communication, embolize to the systemic arterial circulation, and affect the CNS. If right-to-left shunts did not occur, these clots would presumably embolize to the lungs and spontaneously lyse or, being very small relative to lung volume, would not cause any significant clinical sequelae. Although large venous emboli have been shown on TEE or at surgery to cross and be trapped in a PFO, most cryptogenic strokes are small and are probably caused by platelet plugs or venous emboli that are 1 to 3 mm in diameter (Figure 2). The incidence of using phlebography to find deep vein thrombosis after cryptogenic stroke has been less than 10%; however, a recent study involving MR...
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PFO closure was performed at our institution between 2001 and 2005 for secondary prevention of stroke. Although these nonrandomized trials do not prove that percutaneous closure of PFO is preferable to medical management, these comparisons are intriguing and underscore the importance of performing prospective, multicenter, randomized trials.

One study demonstrated that among patients who have a PFO without evidence of paradoxical embolization, the relative risk of ischemic strokes associated with a PFO decreases with age as other risk factors for stroke become more likely, according to one study. The prevalence of PFO in patients with ischemic cryptogenic stroke who are younger than 55 years was 43%, compared with 21% for those older than 55 years.

Differing hypotheses for the cause of stroke or different methods of identifying a PFO may explain the different observations seen in various studies. A retrospective subanalysis of the PICSS found that the presence of a PFO significantly increased the risk of adverse events in patients older than 65 years (2-year event rates, 37.9% vs 14.5% for controls without a PFO; \( P = .01 \)) but not in patients younger than 65 years (2-year event rates, 10.0% vs 13.9% for controls without a PFO; \( P = .15 \)). Several studies have shown that patients with cryptogenic stroke are more likely to have large PFOs and more extensive right-to-left shunting.

Currently, there are no treatment recommendations for patients who have a PFO without evidence of paradoxical embolization. A person’s risk of having a stroke if he or she has a PFO is estimated to be 1 in 1000. Treatment options for patients who have had a cryptogenic stroke or a transient ischemic attack and who also have an interatrial communication are more complex and controversial. The 4 treatment choices for such patients are medical therapy with antiplatelet agents, medical therapy with anticoagulants, surgical closure, and transcatheter closure of the interatrial communication.

The rate of recurrent neurologic events with medical therapy is high (about 2% to 8% per year). In the Warfarin-Aspirin Recurrent Stroke Study, no significant difference was seen in the rates of recurrent events in those patients who had experienced a cryptogenic stroke who were treated with aspirin and those who were treated with warfarin. In another randomized trial, clopidogrel (Plavix, Bristol-Myers Squibb) plus aspirin did not reduce the rate of recurrent stroke compared with clopidogrel alone.

Both percutaneous and surgical closures of interatrial communications have been associated with high success rates and minimal complication rates. They also have been associated with very low risk of recurrent neurologic events compared with historical controls and nonrandomized cohorts. In a large meta-analysis of 10 studies of percutaneous PFO closure and 6 studies of medical therapy for secondary prevention of neurologic sequelae in patients with cryptogenic stroke (total of 2490 patients), the 1-year rate of recurrent neurologic thromboembolism associated with transcatheter intervention was 0% to 4.9%, and the incidence of major and minor complications was 1.5% and 7.9%, respectively. Medical management was associated with a 1-year recurrence rate of 3.8% to 12.0%.

One study demonstrated that among patients who have PFO closure for presumed cryptogenic stroke, younger patients (younger than 45 years) appear to benefit more than older patients. Transcatheter closure of a PFO in patients who also have an ASA did not result in more complications than transcatheter closure in patients who only have a PFO. No recurrent neurologic or embolic events have occurred during an average follow-up of 2 years for a cohort of 110 patients in whom a PFO closure was performed at our institution between 2001 and 2005 for secondary prevention of stroke. Although these nonrandomized trials do not prove that percutaneous closure of PFO is preferable to medical management, these comparisons are intriguing and underscore the importance of performing prospective, multicenter, randomized trials.

To date, no randomized trial has been completed that compares the efficacy of percutaneous closure
of interatrial communications with medical therapy for the secondary prevention of neurologic events. Two randomized trials are in progress and are expected to be completed in 2 years. The Quality Standards Subcommittee of the American Academy of Neurology recently published their practice parameters for recurrent stroke with PFO and ASA. They concluded that “a PFO is not associated with increased risk of subsequent stroke or death among medically treated patients with cryptogenic stroke. However, both PFO and ASA possibly increase the risk of subsequent stroke (but not death) in medically treated patients younger than 55 years. In patients with a cryptogenic stroke and an atrial septal abnormality, the evidence is insufficient to determine if warfarin or aspirin is superior in preventing recurrent stroke or death, but minor bleeding is more frequent with warfarin. There is insufficient evidence to evaluate the efficacy of surgical or endovascular closure.” So that this issue can be definitively addressed, neurologists and cardiologists are strongly encouraged to enroll patients with PFO who have had a cryptogenic stroke into one of the randomized trials that currently are evaluating the efficacy of PFO closure for the secondary prevention of stroke. The Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial is testing the Amplatzer PFO occluder (AGA Medical Corporation, Golden Valley, MN) and the CLOSURE I trial is evaluating the STARFlex device (NMT Medical, Boston).

MIGRAINE AND INTERATRIAL COMMUNICATIONS

Migraine affects approximately 12% of the population (18% of females and 6% of males). The annual cost of labor lost to migraine disability is estimated to be between $5.6 billion and $17.2 billion. Migraine headache with aura is a risk factor for the development of stroke, especially in women. Despite medical advances in the treatment of migraine, many patients suffer frequent and disabling episodes. Several studies have highlighted an association between PFOs and migraine headaches. The incidence of interatrial communications, primarily PFOs, appears to be increased in patients with migraine, especially in patients who experience migraine with aura. A recent study by Anzola and colleagues reported the prevalence of PFO to be 48% in patients who have migraine with aura, compared with 23% in patients who have migraine without aura and 20% in controls (P = .01). Another study that investigated the association between PFO and symptomatic migraine in patients with cryptogenic stroke found that 52% of the patients in whom a PFO was thought to play a causal role in the stroke had migraine with aura. In comparison, only 16% of patients in whom the PFO was determined to be unrelated to the stroke were prone to migraine with aura.

In addition, in the patient enrollment phase of the Migraine Intervention with STARFlex Technology (MIST) trial, which is being conducted in Britain, interatrial communications were found in 60% of migraineurs enrolled in the study, compared with 27% in the general British population. Moreover, 40% of the enrolled patients had a large atrial shunt, compared with 7% in the general British population. The MIST trial is a randomized blind trial evaluating the efficacy of PFO closure compared with standard medical therapy for treatment of migraine headache. Closure of interatrial communications may result in improvement of migraine headaches. Six independent nonrandomized series show a relationship between closure of interatrial communications and their effect on migraine headache; the results of these studies are summarized in the Table. PFO closure in these trials was performed primarily for secondary prevention of stroke. Although a different methodology was used for assessment of migraine severity and the follow-up time was different in each study, all 6 reports demonstrated a comparable improvement in severity and frequency of migraine. The average prevalence of migraine was 35% in these studies. After interatrial communication closure, migraine headache episodes completely ceased in 29% to 80% of patients. In 70% to 80% of the patients, migraines resolved or significantly improved in frequency and severity. Never has there been a medical treatment of migraine with such impressive results. In a recent study performed at our institution, 37 (42%) of 89 patients undergoing percutaneous closure of an interatrial communication primarily for the secondary prevention of stroke or closure of ASD were migraineurs. Migraine headache was common in 45% of patients with PFO and 30% of patients with ASD. At 3 months after closure of the interatrial communication, episodes of migraine headache had ceased in 22 (60%) of 37 patients. Among the 24 patients who experienced migraine with aura, 18 (75%) had complete resolution. Of the 13 patients who experienced migraine without aura, 4 (31%) had complete resolution. Of the remaining patients, 40% experienced significant improvement (greater than or equal to 2 grades on the Migraine Disability Assessment Questionnaire) in frequency and severity of migraine headache (Table). The benefit has been sustained in this population over a median follow-up period of 18 months.
Based on information about the association between PFO, cryptogenic stroke, and migraine, several new hypotheses have been proposed for the cause of migraine headache. Migraine headache is thought to be caused by a small venous embolus that crosses the PFO paradoxically and passes into the cerebral circulation. Rather than inducing a stroke, the small embolus or platelet plug precipitates a spreading wave of depolarization that constitutes the neurologic phenomenon of migraine. A recent study supports this theory; researchers found a 13.7-fold higher incidence of MRI lesions in migraine patients with aura compared with controls.

Alternatively, we hypothesize that migraine is precipitated in susceptible persons by chemical substances that can pass directly through the atrial shunt before they can be detoxified or diluted in their first passage through the lungs. These substances, in elevated concentrations, could cause migraine in susceptible persons without a PFO. However, if a PFO is present, these substances could potentially shunt from the venous to the arterial system and reach the brain in a more concentrated packet than if a central shunt were not present. In this hypothesis, the presence of a PFO also predisposes a person to paradoxical embolism and stroke and is the pathway for emboli that may produce the lesions seen on MRI in patients with migraine. "Migraine stroke" may not be induced by intense vasospasm; rather, it probably is a manifestation of a paradoxical embolism through a PFO.

Prospective randomized trials are under way to determine whether closure of PFO in patients with migraine leads to significant reduction in the incidence of migraine compared with medical therapy. The MIST trial had already enrolled 370 patients as of May 2005. A multicenter, randomized, double-blind trial of the Amplatzer PFO occluder versus standard medical therapy for treatment of migraine headache is currently under evaluation by the FDA. These clinical trials should determine whether the association between migraine and PFO is causal and whether closure of interatrial communications will become a primary treatment to alleviate migraine headache.

**PLATYPNEA-ORTHODEOXIA SYNDROME**

Platypnea-orthodeoxia is a rare and poorly understood syndrome in which dyspnea and arterial desaturation develop in patients who are in the upright position. The disorder is caused by orthostatic accentuation of a right-to-left shunt across an interatrial communication, usually a PFO. The syndrome most commonly occurs in patients with a history of a major pulmonary disorder, such as recurrent pulmonary emboli or chronic lung disease, and in patients in whom a pneumonectomy has been performed. Pulmonary artery pressures are typically normal. The physiologic mechanism is unknown. Transcatheter closure of the interatrial communication has resulted in increased arterial saturation and improved respiratory function.

**NEUROLOGIC DECOMPRESSION IN DIVERS**

Neurologic decompression illness is caused by formation of free gas bubbles from tissues as the diver ascends to the surface. The free gas bubbles can compress organs, block venous or arterial flow, or lead to activation of inflammatory or clotting cascades. Symptoms may be mild and include fatigue, malaise, sense of foreboding, arthralgias, lymphadenopathy, and pruritus (type 1 decompression sickness). Patients with more extensive decompression illness (type 2) may exhibit neurologic and pulmonary manifestations. The neurologic insult may involve the spinal cord (especially the lower thoracic spinal cord) or the cerebrum. Neurologic symptoms may include paresthesias, paraplegia, urinary and bowel incontinence, ataxia, memory loss, speech and visual disturbances, or change in personality. The pulmonary manifestations include dyspnea, wheezing, chest pain, and pharyngeal irritation. Neurologic decompression illness can cause death if untreated. The incidence of PFO appears to be increased in patients with neurologic decompression illness.

Conversely, the risk of neurologic decompression illness is much higher in persons with PFO than it is in controls. In one study, the presence of a PFO increased the risk of decompression illness events in divers by 4.5-fold \( P = .03 \) compared with divers without a PFO. Furthermore, almost twice as many ischemic brain lesions were seen in divers with PFO as in divers without PFO \( P = .07 \). In another study of sport divers, multiple brain lesions were associated with the presence of a large PFO, even in asymptomatic individuals. Transcatheter closure of PFO has been successful in preventing recurrence of neurologic decompression sickness in divers.

**TECHNICAL ASPECTS OF PERCUTANEOUS CLOSURE**

Although both surgical repair and percutaneous closure of PFO yield excellent results, percutaneous closure is currently the modality of choice. In the United States, percutaneous closure of a PFO is permitted by the FDA only under a Humanitarian Device Exemption protocol supervised by the local institutional review board. Technically, it is simple to perform and associated with very high success rates and minimal short- and long-term complications. The procedure can be performed safely on an outpatient with mild conscious sedation. At many institutions, patients are...
discharged on the same day.\textsuperscript{13,78}

Although there is no controlled study of postprocedure anticoagulation, aspirin (325 mg/d) and clopidogrel (75 mg/d) are usually prescribed for discharged patients for 1 to 3 months. Standard prophylaxis against bacterial endocarditis also is prescribed. Although there are only 3 reported cases of endocarditis in relation to approximately 60,000 implanted devices, there is a risk that a permanent implanted foreign body will act as a nidus for microorganisms. Management of infection would require surgical explantation.

The majority of ostium secundum ASDs can be closed percutaneously.\textsuperscript{24} Patients with large ASDs (more than 38 mm), as well as all patients with ostium primum ASDs or sinus venosus ASDs, require surgical repair. The majority of ostium primum ASDs or sinus venosus ASDs require surgical repair in children for hemodynamic purposes but are not commonly encountered in the adult population. The ideal percutaneous closure device should be one that is technically simple to deploy and that has an excellent success rate, eliminates all residual shunting, and is durable with negligible risk of dislodgement or device failure. The device should not create an adverse inflammatory response or thrombus formation and should not increase the risk of future subacute bacterial endocarditis.

There are currently several devices available for the closure of a PFO in the United States under the Humanitarian Device Exemption. These include the Amplatzer PFO occluder (Figure 3) and the CardioSEAL (NMT Medical) and STARFlex devices. In the United States, only the Amplatzer septal occluder is available for closure of ASD.

Although the PFO closure devices have excellent acute and long-term results, the CardioSEAL and STARFlex devices have been associated with a high rate of thrombus formation (22% at 1 month postprocedure by TEE in one study).\textsuperscript{22,28} This may explain the incidence of postclosure emboli in some series. The Amplatzer PFO occluder has not been associated with thrombus formation; however, rare cases of device erosion into the left atrial wall and aorta have been reported.\textsuperscript{79} Such an event requires open heart surgery and can result in death. The presence of a residual shunt after closure has been reported in 5% to 10% of cases in most studies with either the Amplatzer PFO occluder or the CardioSEAL and STARFlex closure devices,\textsuperscript{28,80} but most of these are minimal.

THE FUTURE

Currently, several companies are developing newer approaches to PFO closure that address the complications being seen. These techniques include percutaneously suturing the PFO flap or cautering it with radiofrequency. If these techniques prove effective, they may reduce the complications associated with a permanent implant. This will make the procedure more acceptable for conditions less severe than cryptogenic stroke, such as migraine and PFO, which affect an estimated 13 million Americans.*

REFERENCES


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