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EXPEDITED REVIEW **State-of-the-Art Paper**

Patent Foramen Ovale: Current Pathology, Pathophysiology, and Clinical Status

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Patent foramen ovale (PFO) is experiencing increased clinical interest as a congenital cardiac lesion persisting into adulthood. It is implicated in several serious clinical syndromes, including stroke, myocardial infarction, and systemic embolism. The PFO is now amenable to percutaneous interventional therapies, and multiple novel technologies are either available or under development for lesion closure. The PFO should be better understood to take advantage of emerging percutaneous treatment options. This paper reviews PFO anatomy, pathology, pathophysiology, and clinical impact and discusses current therapeutic options. (J Am Coll Cardiol 2005;46:1768–76) © 2005 by the American College of Cardiology Foundation

Patent foramen ovale (PFO) is experiencing much clinical interest as a congenital cardiac lesion that persists into adulthood (1,2). It is a risk factor for several serious clinical syndromes, including paradoxic systemic embolism, such as ischemic stroke (3), myocardial infarction (4), decompression sickness (DCS) in divers (5–7), and complications of pulmonary embolism (8). Recent evidence further implicates PFO as a possible cause of migraine headache through mechanisms not yet understood. The PFO is now amenable to interventional percutaneous therapy (9), and multiple novel technologies are either available or under development for lesion closure. The PFO pathology, pathophysiology, and clinical impact should be better understood as multiple approaches to percutaneous closure become available for clinical application. This paper reviews current knowledge of this interesting lesion and summarizes future therapeutic directions.

PFO EMBRYOLOGY

The foramen ovale is necessary for blood flow across the fetal atrial septum. Beginning at four weeks of pregnancy the primordial single atrium divides into right and left sides by formation and fusion of two septa: the septum primum and septum secundum (Fig. 1) (10). The septum primum is at first crescent-shaped, creating a large window connecting the left and right atrium. It grows from the primordial atrial roof toward the endocardial cushions, partially dividing the common atrium into right and left halves. The endocardial cushions are formed on the dorsal and ventral walls of the atrioventricular canal, approach each other, and fuse, dividing the atrioventricular canal into right and left sides. The foramen primum results, allowing oxygenated blood flow from the right to the left atrium. As the septum primum grows toward the endocardial cushions, perforations develop. These perforations form a large central window, through programmed cell death, before the septum primum and endocardial cushions fuse.

The window made as these perforations fuse is the foramen secundum, which also supplies shunt blood flow from the right to the left atrium. On the right side of the septum primum, another crescent-shaped membrane grows from the ventrocranial atrial wall: the septum secundum. It gradually grows and overlaps part of the foramen secundum, forming an incomplete septal partition as an oval-shaped window. It is this window that becomes the foramen ovale. The remaining septum primum forms a flap-like valve over the foramen ovale, which typically closes by fusing with the growing septum secundum after birth.

As oxygenated blood flow in utero from the inferior vena cava enters the right atrium, it crosses the patent foramen ovale and becomes the systemic circulation. Most blood flow from the superior vena cava is routed through the tricuspid valve and enters the right ventricle. At birth, right heart pressure and pulmonary vascular resistance drop as pulmonary arterioles open in reaction to oxygen filling the alveolus. Left atrial pressure may also rise as the amount of blood returning from the lungs increases. Either or both of these mechanisms may cause flap closure against the septum secundum. This fusion is complete by age two in about 75% of individuals, but patency occurs in the other 25%. It is a residual, oblique, slit-shaped defect resembling a tunnel. The reasons PFOs fail to close are unknown, but they likely relate to multifactorial inheritance (11).

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Abbreviations and Acronyms

ASA = atrial septal aneurysm
ASD = atrial septal defect
DCS = decompression sickness
INR = international normalized ratio
MRI = magnetic resonance imaging
PFO = patent foramen ovale
TCD = transcranial Doppler
TEE = transesophageal echocardiography
TIA = transient ischemic attack
TTE = transthoracic echocardiography

PFO ANATOMY

The autopsy-derived prevalence of probe-patent PFO is about 27%, with decreasing prevalence at each decade of life (Table 1) (12). Patent foramen ovale slit width in the adult ranges from 1 to 19 mm (mean 4.9 mm), derived from postmortem formalin-fixed specimens. Figure 2 shows the gross anatomy of the PFO. The PFO size increases with each decade of life. The mean diameter in the first decade is 3.4 mm and in the tenth decade is 5.8 mm, perhaps reflecting size-based selection over time where larger PFOs remain patent and smaller defects close. Greater PFO size increases the risk of paradoxic embolism (13,14). Heterogeneity of size and morphology are pertinent to interventional device closure selection (15).

Table 1. Patent Foramen Ovale Incidence Versus Age (12)

1–29 yrs	30%
30–79 yrs	25%
≥80 yrs	20%

PFO ASSOCIATIONS: ATRIAL SEPTAL ANEURYSM AND CHIARI NETWORKS

Atrial septal aneurysm. The PFO is associated with several anatomic anomalies. A common association is atrial septal aneurysm (ASA), where part or all of the atrial septum shows aneurysmal dilatation (16), protruding into either atria (17). The ASA is defined as phasic septal excursion of at least 15 mm during the cardiorespiratory cycle (18). The prevalence of ASA is 1% in autopsy-based studies (19), a number differing from echocardiographic studies. One transthoracic echo study found an ASA in 0.22% of patients (18), and another reported a 1.9%

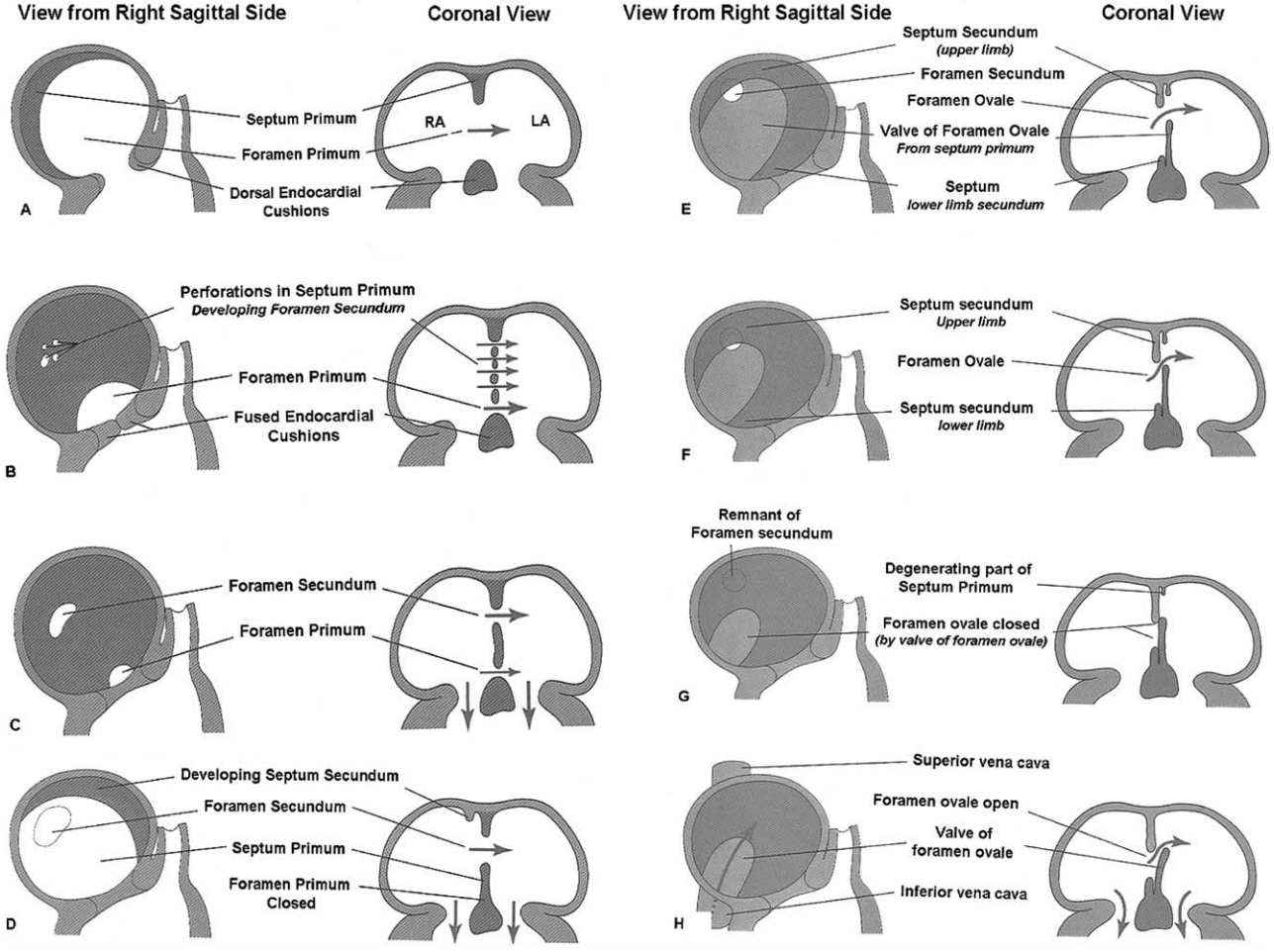

Figure 1. Diagrammatic representation of patent foramen ovale development from embryology. Right sagittal and coronal views. Adapted from Konstantinides et al. (8). LA = left atrium; RA = right atrium.

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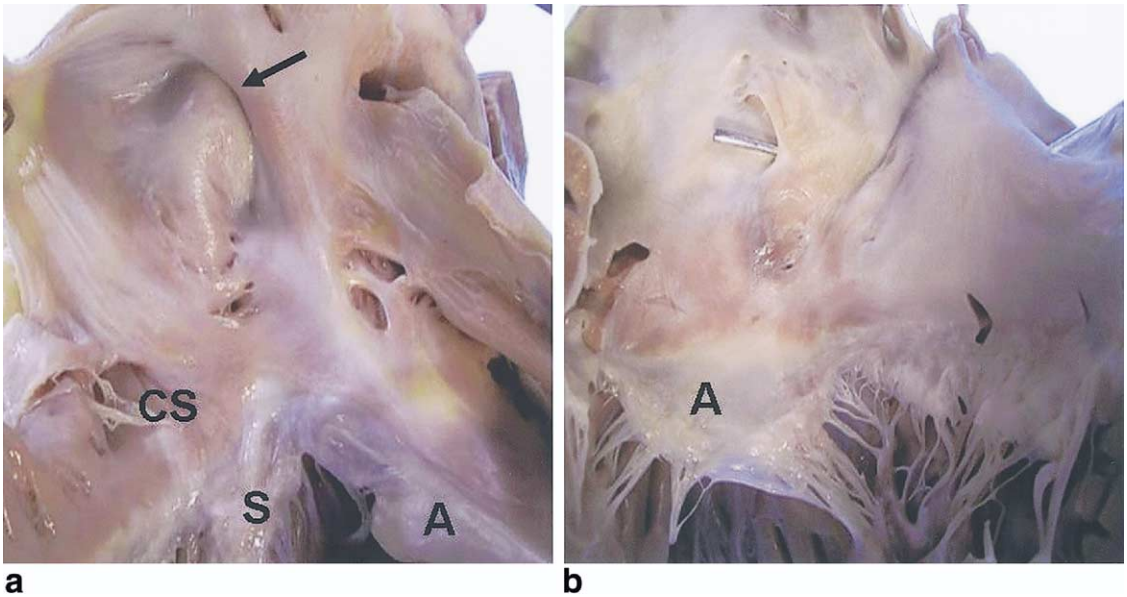

Figure 2. Gross anatomy of the patent foramen ovale. **(a)** View from the right atrium showing a patent foramen ovale. Patency is determined by probing. The limbus **(arrow)** is seen forming a rounded cuff around the valve of the foramen ovale. The anatomic locations relative to the coronary sinus (CS) and tricuspid valve (S = septal leaflet; A = anterior leaflet) can be appreciated. **(b)** Same case viewed from the left atrium with probe demonstrating patency. The anterior leaflet of the mitral valve is seen below the probe.

prevalence using a definition of more than 10 mm excursion (16). M-mode transesophageal echocardiography (TEE) or intracardiac echocardiography is essential for precisely measuring septal excursion in ASA.

The prevalence of ASA is higher when examined by TEE. One biplane TEE study reported ASA prevalence as 2.2% and another reported 4% (20,21). In echocardiographic studies of stroke patients, the prevalence is substantially increased. Atrial septal aneurysm was found in 7.9% of stroke patients by biplane TEE (20) and 15% by single-plane TEE (21).

Patent foramen ovale was detected by TEE using contrast or Doppler color in 70% of ASA patients (17), suggesting that PFO detection is possible by intracardiac echocardiography. Intracardiac echocardiography may be more comfortable for the patient, and the Valsalva maneuver easier during this procedure. However, it is more invasive (with potential complications) and more costly, and systematic evidence-based recommendations have not yet been established (22). Moreover, TEE may have better resolution.

A study in adults showed that 33% of patients with ASA also had PFO, although 32% had isolated ASA (23). Thus, ASA is more frequent in subjects with PFO, and ASA predicts PFO. The odds of PFO are 4.6 times greater with ASA than without ASA (20). Atrial septal aneurysm is more frequent in stroke patients, but it is also more common in patients with PFO, making cause or effect uncertain.

Chiari networks. The Chiari network is a remnant of the right valve of the sinus venosus, and its role is poorly understood (24). It originates from a region of the eustachian and thebesian valves with attachment to the upper wall of the right atrium or atrial septum. The eustachian valve is common but should be distinguished from Chiari networks because it does not attach to the upper wall of the right atrium or atrial septum, although it may be mobile and fenestrated. The prevalence of the Chiari network is 2% to 3% in one autopsy study (25). A recent study using TEE with contrast suggested the clinical importance of Chiari networks (26). In 1,436 consecutive adult patients, 29 had confirmed Chiari networks (prevalence, 2%). This study found a frequent association between Chiari networks and PFO, with 83% of patients affected by both. Large right-to-left shunting was found significantly more often in patients with Chiari networks than in controls (55% vs. 12%, $p < 0.001$). This study also found Chiari networks associated with ASA in 24% of patients. The Chiari network is more common in cryptogenic stroke patients than in patients evaluated for other indications (4.6% vs. 0.5%), and it may facilitate paradoxic embolism.

PFO MICROANATOMY

Little has been published about PFO histopathology, a point of increasing importance as percutaneous closure technologies are being developed that must interact with these tissues at cellular levels. Figures 3 to 5 show microanatomy of both patent (Figs. 3 and 4) and closed foramen ovale (Fig. 5). The muscular atrial wall consists of endocardium having endothelium and thick subendothelial layers of connective tissue rich in collagen and elastin. A thicker myocardium lies beneath these structures, with loosely arranged musculature. The epicardium covers the heart and is lined externally by a single layer of mesothelium.

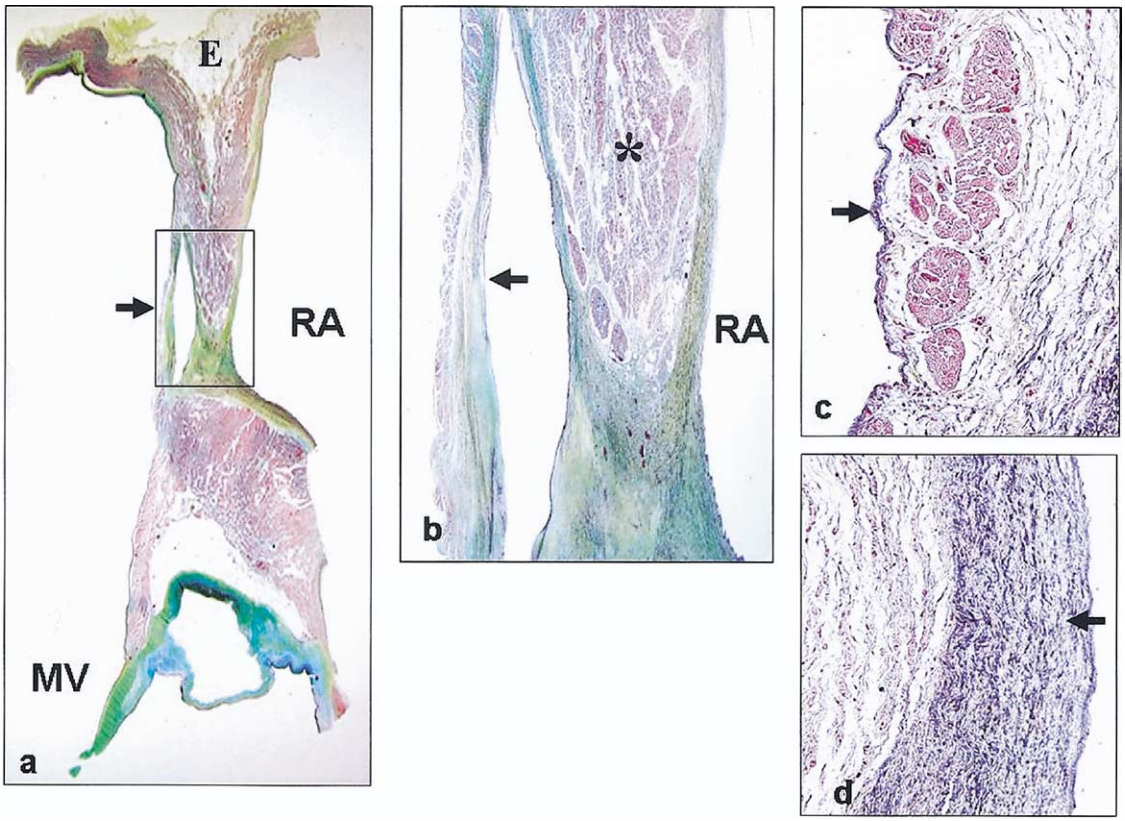

Figure 3. Histopathology of the tissue membranes constituting a patent foramen ovale. **(a)** Longitudinal section of the atrial septum, showing a patent foramen ovale **(box)** with valve **(arrow)**. The superior epicardial surface (E) and a portion of the mitral valve (MV) are also seen. The septal wall consists predominantly of myocardium and adipose tissue. RA = right atrium. **(b)** A higher magnification of **boxed area in panel a**, showing the valve with a thickened fibrotic right endocardial surface **(arrow)**. The atrial septum **(*)** in this region consists of myocardium and becomes predominantly fibrotic inferiorly. Movat ×1.25. **(c)** A higher magnification of the valve from the left side, showing a relatively thin endocardial surface **(arrow)**. The underlying myocardium is composed of bundles of cardiac myocytes. Movat ×20. **(d)** A higher magnification of the valve from the opposite side (right), highlighting the endocardial surface **(arrow)**, which consists of a thick layer of collagen and elastic fibers. Movat ×20.

PFO DETECTION

Patent foramen ovale may be detected by transthoracic echocardiography (TTE), TEE (27,28), transcranial Doppler (TCD) (29), and sometimes by transmitral Doppler (30). These techniques were compared in studies of proven embolic stroke. One study revealed that TEE detected PFO most sensitively, showing a prevalence of 39%. In this study, TTE found PFOs in 18% and TCD found 27% (31). All PFOs detected by TTE and TCD were also detected by TEE. Six PFOs that could not be detected by TCD were <2 mm in size by TEE, implying that TCD may miss small defects. Patent foramen ovale detection can be augmented by cough or releasing a sustained Valsalva maneuver. It opens the foramen when the right atrium fills with blood from the abdomen, while the left atrium is volume depleted prior to blood passing through the pulmonary circulation (9). One TTE study showed that right-to-left shunting through PFO increased when subjects performed the Valsalva maneuver compared to rest (18% vs. 5%) (32). This maneuver is now considered necessary to find right-to-left shunts when performing echocardiography of any type, with or without contrast injection. The physical hole in the atrial wall may not be imaged, but detecting its shunt clearly improves sensitivity and specificity.

Transcranial Doppler is comparable to contrast TEE for detecting PFO-related right-to-left shunts (type A, class II evidence) (33), and is easy to perform at the bedside. One study compared the sensitivity of transcranial color-coded sonography with TEE for detecting cardiac right-to-left shunts. It found that transcranial color-coded sonography is a sensitive noninvasive method for detecting right-to-left cardiac shunts, as sensitive as contrast TEE (34). Transcranial Doppler has recently been augmented by power M-mode, a new technology allowing power display with Doppler velocity and frequency signals over selectable depth ranges along the transducer beam (35). Transcranial Doppler M-mode enhances sensitivity to contrast bubble emboli over single-gated TCD examination (36).

PFO: ASSOCIATED CLINICAL SYNDROMES

Cryptogenic stroke. Approximately 40% of ischemic strokes have no clear etiology and are therefore termed cryptogenic. One study of 60 adults under 55 years of age with ischemic stroke compared contrast echocardiographic

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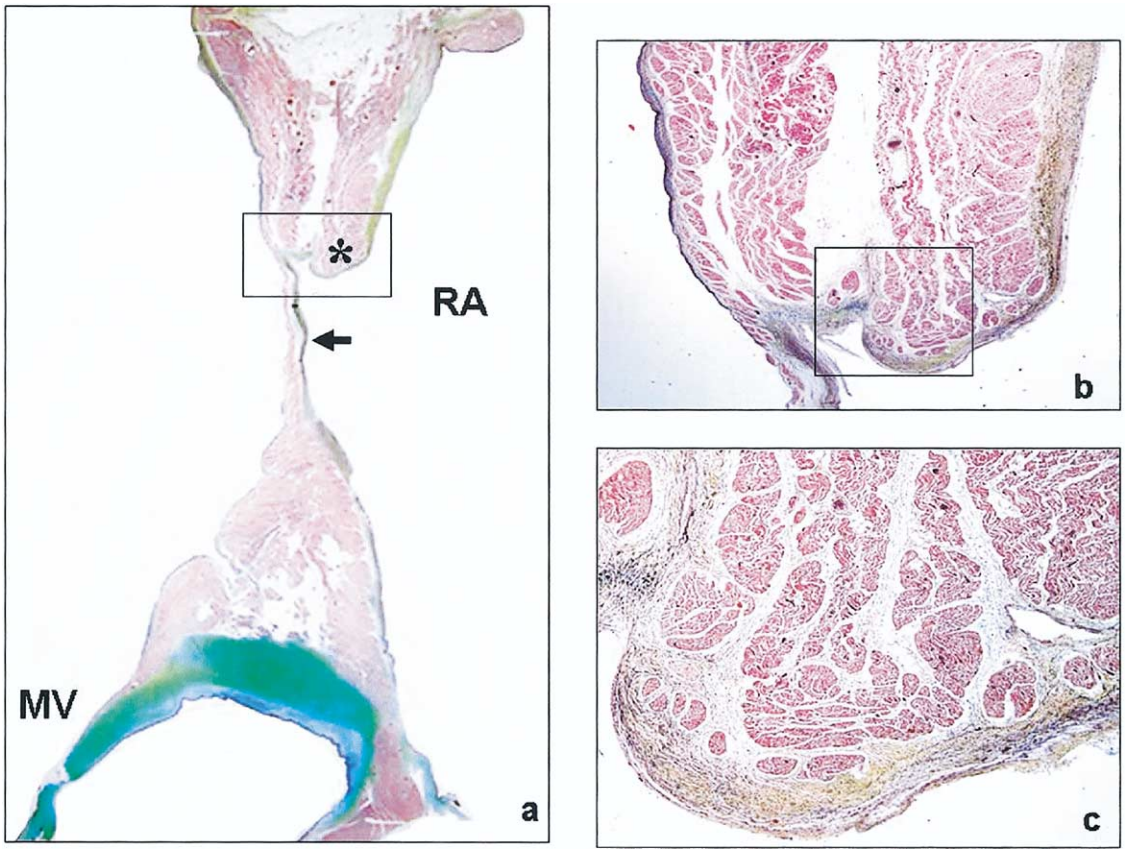

Figure 4. **(a)** Posterior longitudinal section of the atrial septum from the same case shown in Figure 3. The limbus **(*)** and valve **(arrow)** of the foramen ovale are indicated. A portion of mitral valve (MV) is seen at the inferior margin. **(b) Boxed area** demonstrates the area where the limbus attaches to the valve of the foramen ovale. Note the thick endocardial layer of the limbus and underlying myocardium separated by wide connective tissue bands. Movat ×1.25. **(c)** A higher magnification of the **boxed portion** of the limbus in **panel b** characterized by a thickened endocardial surface rich in collagen and elastic fibers. Connective tissue bands are seen separating myocyte bundles. Movat ×4.

examinations with 100 normal subjects. Patent foramen ovale prevalence was significantly higher in the stroke group (40%) than in controls (10%) ($p < 0.001$). Patent foramen ovale was found in 26 stroke patients (54%) with no other identifiable cause, and the study concluded that PFO-induced paradoxic embolism is a cause of stroke (37). The PFO-ASA Study supports these findings, where 46% of young cryptogenic stroke patients had PFO (38). Cramer et al. (39) evaluated young stroke patients (18 to 60 years old) early after stroke using magnetic resonance imaging (MRI) venography. Pelvic deep venous thrombosis was increased in the cryptogenic stroke population compared to controls (20% vs. 4%). The cryptogenic stroke group was significantly younger (42 vs. 49 years) with fewer risk factors for atherosclerosis, such as hypertension (73% vs. 26%) and smoking (17% vs. 7%). Patent foramen ovale prevalence was significantly higher in the cryptogenic stroke group than in controls (59% vs. 19%).

A prospective study of 598 patients (ages 18 to 55 years) presenting with cryptogenic stroke showed that 36% had PFO, 1.7% had ASA, and 8.5% had both abnormalities. Patients with both PFO and ASA who have had a stroke, are thus at higher risk for recurrent stroke, and preventive strategies other than aspirin should be considered (40).

The platypnea-orthodeoxia syndrome. The platypnea-orthodeoxia syndrome comprises both dyspnea (platypnea) and arterial desaturation in the upright position with improvement in the supine position (orthodeoxia). It is uncommon, but several dozen cases are reported (41). Two components must coexist to create this syndrome (42). One is an anatomic defect and the other functional. The anatomic component must have an interatrial shunt, such as an atrial septal defect (ASD), PFO, fenestrated ASA, or intrapulmonary shunting.

A functional component induces the deformity in the atrial level and may occur while rising to an upright from a recumbent position. Cardiac causes also exist, including pericardial effusion, constrictive pericarditis, and toxicity from drugs such as amiodarone (43). Key to this syndrome is right atrial pressure elevation causing right-to-left shunt. Interestingly, blood may flow from right to left at the atrial level even when right heart pressure is normal (44), as typically occurs with persistent eustachian valves. The definitive treatment for platypnea-orthodeoxia is closure of the atrial shunt (45).

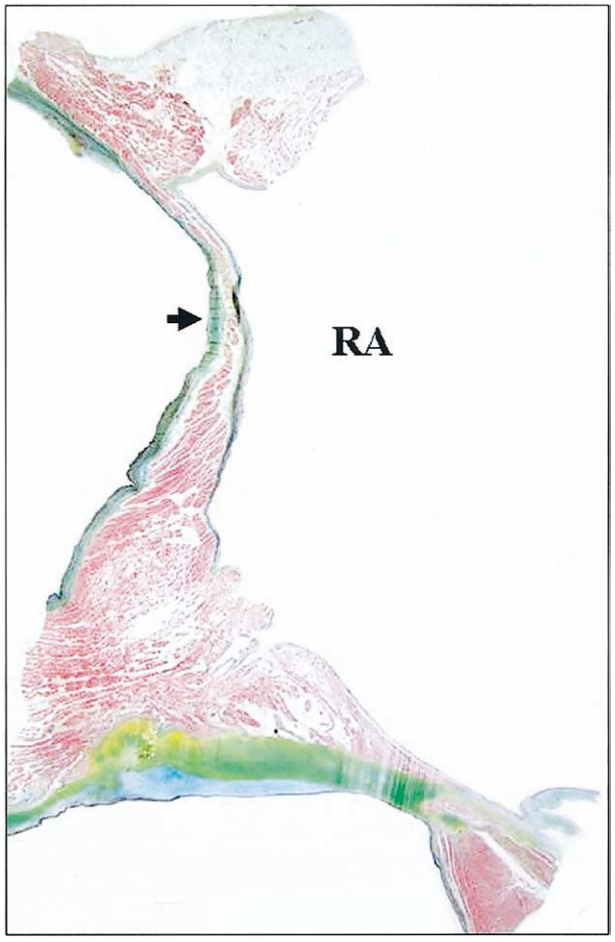

Figure 5. Longitudinal section of the foramen ovale and atrial septum from a heart with closed foramen ovale. The left endocardial surface of the valve is shown by the **arrow**. Note the slightly thickened left endocardial surface **(arrow)** compared to the right side. RA = right atrium.

Embolism from DCS. Arterial gas embolism through an ASD was reported first in a scuba diver in 1986 (5). Type 1 DCS is composed of localized joint pain, musculoskeletal pain, and/or skin rash, and type 2 DCS consists of neurologic symptoms (limb tingling, paresthesias, severe headache with mental confusion, paraplegia, loss of consciousness, audiovestibular symptoms, and dyspnea with chest pain). The PFO at rest is significantly associated with type 2 DCS.

A recent study found a strong relationship between PFO size and DCS in a study of 230 divers (6). Another study demonstrated the functional and anatomic characteristics of PFO with and without DCS (7). This study suggested that DCS was associated with right-to-left shunting at rest. Atrial septal mobility and PFO diameter are also associated with the risk of developing DCS.

Migraine and vascular headache. Migraine and vascular headache may be related to PFO, according to an interesting new series of studies (46). Migraine headache is a benign recurring syndrome of headache, nausea, vomiting, and/or other symptoms of neurologic dysfunction. Over 2,500,000 patients in the U.S. have at least one migraine headache weekly, with a lifetime prevalence of 18%. Migraine is a risk factor for cryptogenic stroke, especially in young patients without atherosclerotic risk factors. Vascular headache is generally attributed to a cranial or cervical vascular disorder and is classed as secondary. If paradoxic embolism causes headache, PFO may indeed be related.

One study demonstrated a significant relationship between PFO closure and improvement of migraine (with aura) using TCD. In that study, 5 of 17 patients no longer complained of migraine, 10 of 17 were much improved, and 2 had no change 6 months after PFO closure (47). A further study examined the relationship between PFO and migraine with or without aura (46). Patent foramen ovale prevalence was 48% in migraine patients, 23% in those without migraine, and 20% in controls. The difference between patients with and without migraine and PFO was significant, as was the difference in those with aura and the control group. However, the group without aura did not differ from the control group in PFO prevalence. A recent study demonstrated transcatheter closure of PFO caused complete resolution or marked reduction in migraine frequency (48). In this study, 162 consecutive patients with paradoxic cerebral embolism undergoing transcatheter PFO closure were investigated. Complete migraine resolution occurred in 56% of patients, and 14% of patients reported a significant (>50%) reduction in migraine frequency. Patients reported an 80% reduction in the mean number of migraine episodes per month after PFO closure (6.8 ± 9.6 before closure vs. 1.4 ± 3.4 after closure, $p < 0.001$). Another recent report similarly concluded that transcatheter closure of PFO or ASD in patients with migraine headaches led to migraine resolution or significant improvement in the majority (76%) of 89 adult patients (49).

The relationship between headache and right-to-left shunt remains poorly characterized. Larger studies of PFO and headache are underway, as are randomized trials of PFO closure and migraine headache relief.

PFO TREATMENT

Medical therapy: recurrent stroke and paradoxic embolism. It is uncertain whether anticoagulants such as warfarin and antiplatelet agents are effective as primary or secondary therapy in preventing stroke among patients with patent foramen ovale (50). The Lausanne Stroke Registry compared aspirin to oral anticoagulation in patients with PFO and cryptogenic stroke (51). This study investigated 92 patients treated with aspirin (250 mg/day) and 37 patients treated with oral anticoagulation (target international normalized ratio [INR] = 3.5). Eight patients changed regimens from oral anticoagulation to antiplatelet agents after three months. The annual cerebrovascular event recurrence was 1.9% for cerebrovascular attack and 3.8% for combined transient ischemic attack (TIA) and attack during

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Table 2. Percutaneous PFO Closure Devices

Device Name	Design	Manufacturer
Rashkind PDA Umbrella	Double umbrella	Bard Billerica, MA
Buttoned Device	Square occluder button	Custom Medical Devices Amarillo, TX
ASDOS	Two self-opening umbrellas	Osypka Corp. Grenzach-Wyhlen, Germany
Angel Wings	Two interconnected squares	Microvena Inc. Vadnais, MN
CadioSEAL	Non-centering double umbrellas	NMT Medical Boston, MA
StarFLEX	Self-centering double umbrellas	NMT Medical Boston, MA
Amplatzer	Self-centering double discs	AGA Medical Golden Valley, MN
Helex	Nitinol wire and PTFE covering	WL Gore Flagstaff, AZ
PFO-Star	Two Ivalon square discs	Applied Biometrics Inc. Burnsville, MN

three years of follow-up. No significant difference was found between aspirin- and warfarin-treated patient groups.

Another prospective study examined PFO 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 for high-risk patients, such as those with septal abnormalities. Stroke recurrence was 2.3% in patients with PFO, 0% in patients with atrial septal aneurysm, and 15.2% in those with both aneurysms and PFO (40).

The PFO in Cryptogenic Stroke Study Investigators found no difference in primary end points (recurrent stroke and death) between aspirin and warfarin treatment in PFO patients at two years. This study concluded that larger PFO or atrial septal aneurysms in stroke patients did not increase the chance of adverse events (52).

The Warfarin-Aspirin Recurrent Stroke Study was a prospective trial of 2,206 patients with prior stroke (53). Patients were randomized to aspirin (325 mg/day) or warfarin (target INR 1.4 to 2.8). After two years, there were no significant differences between aspirin and warfarin treatment for recurrent stroke or death. Patients with cryptogenic stroke showed no significant benefit in either treatment group.

Percutaneous transcatheter closure. Many studies report that transcatheter PFO closure is safe and effective, with efficacy ranging from 86% to 100% (54,55). Recurrent neurologic and peripheral embolic events are reported as 0% to 3.8% per year, possibly reflecting incomplete closure (56) or thrombus formation around the device.

Krumsdorf et al. (57) reported 1,000 consecutive patients undergoing ASD and PFO closure using transcatheter devices. Nine different technologies were used (Table 2). The study reported thrombus formation in the left atrium (n = 11), right atrium (n = 6), or both (n = 3) in 1.2% of ASD patients and in 2.5% of PFO patients (p = NS). Thrombus was diagnosed in 14 of 20 patients at four weeks and in 6 of 20 patients later than four weeks. The most frequent thrombus formation occurred on the CardioSEAL device (NMT Medical, Boston, Massachusetts) (7.1%). The StarFLEX device (NMT Medical) had a 5.7% incidence of thrombus formation, the PFO-Star device (Applied Biometrics Inc., Burnville, Minnesota) 6.6%, the ASDOS device (Osypka Corp., Grenzach-Wyhlen, Germany) 3.6%, the Helex device (WL Gore, Flagstaff, Arizona) 0.8%, and the Amplatzer device (AGA Medical, Golden Valley, Minnesota) had no thrombus formation. Several limitations exist to this retrospective review, including the observation that heparin was typically reversed using protamine immediately after the procedure. Also, hematologic screening was not performed before device implant, and often coagulopathies are discovered only after thrombus is detected. Conclusions were that thrombus formation on closure devices is low and usually resolves with anticoagulation therapy.

Anzai et al. (58) described 66 patients with transcatheter closure and found no thrombus on the Amplatzer device, but 22% of patients had thrombus on the CardioSEAL device. This report indicated that most thrombus disappeared or markedly diminished with additional anticoagulation therapy. One patient underwent surgical device explantation owing to progressively increasing thrombus size and mobility despite intensive anticoagulation therapy.

SURGICAL PFO CLOSURE

In the age of excellent percutaneous PFO closure methods and results, surgical closure has become rare. Several investigators reported surgical PFO closure and cerebrovascular event results. Homma et al. (59) described the safety of surgical PFO treatment, but could not prove superiority of surgical approaches to prevent ischemic event recurrence. In their study, 28 patients with cryptogenic stroke underwent TEE looking for PFO. All patients underwent surgical

closure by open thoracotomy because they refused, could not take, or failed warfarin therapy. With a mean follow-up of 19 months, 14% of patients experienced recurrent neurologic events (one stroke, and three transient ischemic attacks). No patient younger than 45 years of age suffered recurrence, whereas 35% of patients age 45 years or more experienced recurrent events ($p < 0.02$). The authors concluded that although PFO is easily repaired in patients with cryptogenic stroke, its closure does not consistently prevent ischemic event recurrence, and recurrence is more common in older patients.

Devuyst et al. (60) described 30 patients with stroke and PFO who had direct surgical closure. These patients were younger (<60 years) and met at least two of the following four criteria: 1) recurrent clinical cerebrovascular events or multiple ischemic lesions on brain MRI; 2) PFO associated with ASA; 3) more than 50 microbubbles counted in the left atrium on contrast TEE; and 4) Valsalva maneuver or cough preceding the stroke. No patient had complications in the perioperative period. At two years of follow-up without antithrombotic treatment, there was no recurrent stroke or TIA, and no new cerebral lesions developed by MRI. Postoperative contrast TEE and TCD showed residual shunt in two patients who had single as opposed to double continuous suture closure techniques.

CONCLUSIONS

The PFO is an important risk factor for TIA and stroke, 40% of which are "cryptogenic." The type and duration of medical therapy needs further evaluation, especially in high recurrence subsets. Percutaneous PFO treatment appears safe and beneficial not only for secondary prevention but also in high-risk patients without stroke. Multiple novel and exciting technologies are emerging for treating PFO percutaneously (61) that promise rapid, safe, and effective PFO treatment. Optimal technology development will require understanding the PFO at histologic, cellular, and tissue levels. Animal models under development may also aid in this process. As new devices reach clinical application, randomized trials comparing the treatment options will aid in establishing cause and effect relationships between PFO and the myriad clinical conditions, including stroke, TIA, and headache.

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