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Patent Foramen Ovale: Its Association with Stroke and Migraine Headaches

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Executive Summary

Patent foramen ovale (PFO) is quite common in the population and has been associated with a number of clinical syndromes including stroke and migraine headaches. For this reason, much attention has been given to both pharmacologic and interventional management of PFOs. However, data are still lacking on the optimal strategy for managing a PFO in a patient who has suffered a cryptogenic stroke. Similarly, we await further data regarding PFO closure as a treatment for migraine headaches, particularly in patients with an aura. Although PFO has been traditionally considered an innocent bystander or epiphenomenon to a number of disorders, the recent focus requires both caution and guarded optimism as clinical trials attempt to discern the role of this common cardiac anomaly in pathologic states.

Introduction

Patent foramen ovale (PFO) is a congenital cardiac anomaly present in 25% to 30% of the population based on autopsy studies [1]. A PFO allows interatrial shunting, and has been associated with a number of clinical syndromes including stroke and more recently migraine headache with aura [2]. We will review the fundamentals of PFO development and diagnosis, as well as its theorized role in the etiology of stroke and migraine headache. Data regarding treatment is discussed, but definitive randomized trials remain ongoing.

Patent Foramen Ovale

Embryology

In the fetal circulation, a patent foramen ovale allows oxygenated blood to flow from the right to left side of the heart. During pregnancy, oxygenated blood from the placenta passes through the inferior vena cava and crosses the PFO to deliver oxygenated blood to the systemic circulation. At birth, when right heart pressure falls and left atrial pressure rises, the septum primum fuses to the septum secundum to close the PFO (Figure 1).

In a significant percentage of the population, PFOs fail to close, resulting in a communication between the right and left atria. Under normal cardiac conditions, pressure is higher in the left atrium than the right, and the septum primum is pressed against the left atrial wall to prevent blood flow through the PFO. However, if pressures rise in the right atrium, such as with cough or valsalva, blood flow from the right to left atrium is possible. Flow has also been demonstrated through PFOs in the absence of valsalva in some studies, although the mechanism is unclear.

The reasons that PFOs fail to close are not fully understood but familial and genetic factors may be important since the presence of PFOs among siblings appears to be higher [3]. Patients with PFOs appear to be more likely to have other cardiac anomalies, particularly atrial septal aneurysms and Chiari networks [4].

Diagnosis

The most common tool for PFO diagnosis is echocardiography. Transesophogeal echocardiogram (TEE) is more sensitive than transthoracic echocardiogram (TTE) and is superior at detecting other cardiac anomalies [5]. PFO detection with TEE can be augmented by injection of agitated saline to allow for visualization of bubbles passing from the right to left atrium. Usually bubbles are injected at rest and then with valsalva to improve detection.

Transcranial Doppler (TCD) has also been used to detect PFOs [6]. A probe is placed above the zygomatic arch over the middle cerebral artery. After injection of contrast (usually agitated saline or contrast with microbubbles), Doppler ultrasound is used to evaluate for bubbles reaching the probe. A positive test results when bubbles reach the probe within a specified time window. TCD has the advantage over TEE of being non-invasive. Some studies have documented comparable sensitivity and specificity to TEE [6] while others have not [7]. TCD is limited, however, compared to TEE in that it cannot provide detailed anatomic information about the size of the shunt and associated defects such as atrial septal aneurysm.

PFOs and Stroke

Types of Stroke

Stroke is one of the leading causes of death and morbidity worldwide. Approximately 85% of cases are ischemic, usually resulting from atherosclerosis and occurring in patients over the age of 65. A minority of cases, however, affect younger patients (usually less than 65) with few risk factors for atherosclerosis and a negative work-up including MRI of the brain and carotid ultrasound. Such cases are termed "cryptogenic" and prevention of recurrent stroke often focuses on cardiac sources of embolism such as PFO.

Theoretical Mechanisms of PFO in Stroke

It has long been hypothesized that PFO can lead to stroke by allowing passage of thrombus from the right side of the heart to the left—so called "paradoxical embolism." For stroke to occur in this manner, four conditions are thought to be necessary: (1) arterial embolism leading to cerebrovascular ischemia, (2) venous thromboembolism, (3) intratrial communication such as PFO, and (4) a gradient favoring right to left shunting. Rarely are all four conditions documented in a patient with stroke and thus paradoxical embolism remains hypothesized as a mechanism but never proven in the patient with a cryptogenic stroke and a PFO. It has also been hypothesized that the PFO tunnel between the right and left atria may itself be a nidus for clot leading to embolism.

Circumstantial evidence that PFOs contribute to stroke can be found in numerous case-control studies. For example, one early study published in 1988 found a PFO by TEE in 54% of patients younger than 55 with cryptogenic stroke compared with 10% among matched controls [8]. Another meta-analysis found an odds ratio of 5.01 for presence of PFO among patients with cryp-

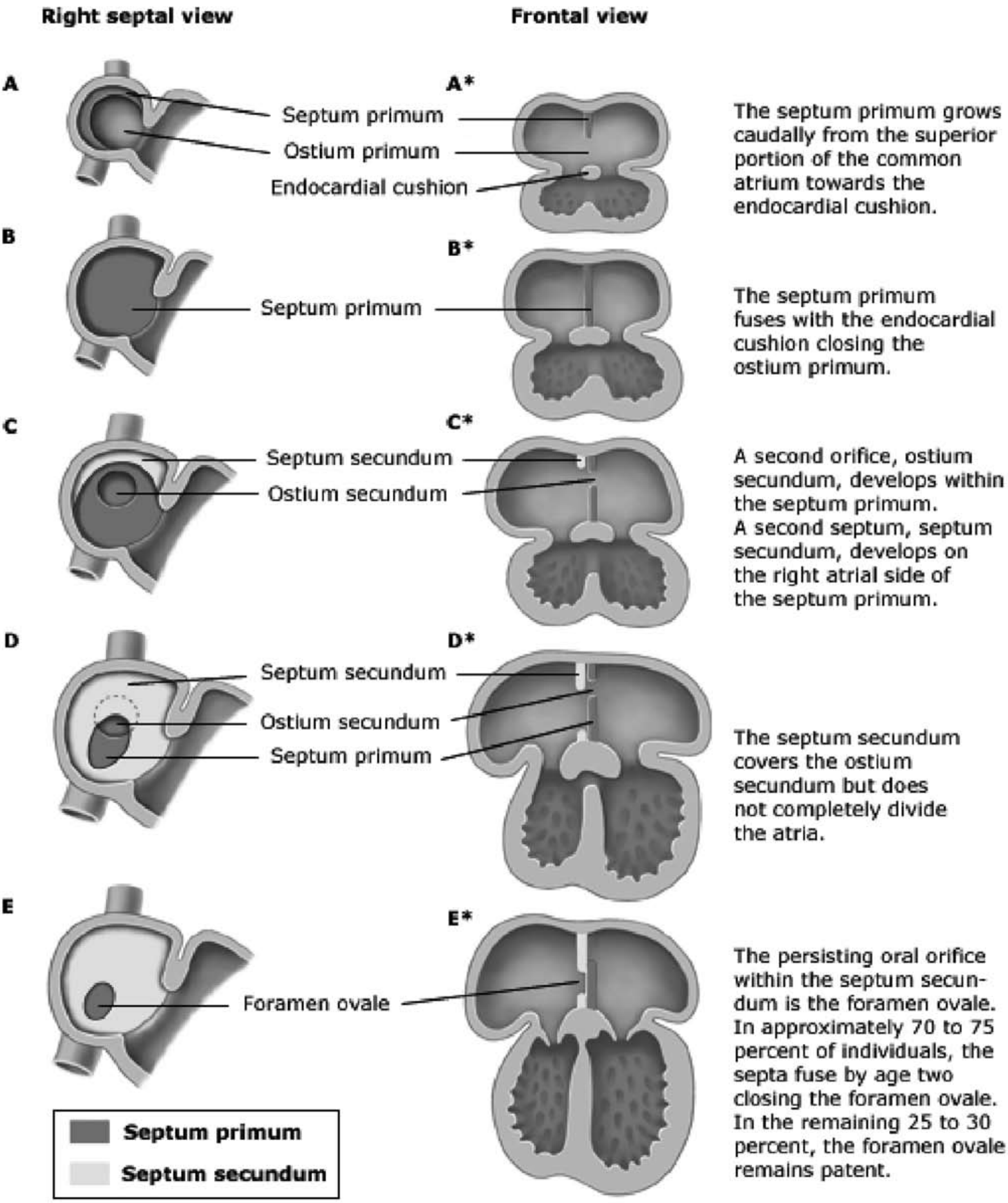

Figure 1
*From Up To Date. Patent foramen ovale. Hidehiko Hara, MD. Robert S Schwartz, MD, FACC

togenic stroke under the age of 55 but not among older patients [9].

This association, however, has been questioned due to several factors. First, few cryptogenic stroke patients report a history of valsalva-type activities prior to their event. Second, venous thromboembolism is rarely detected among these patients, although DVTs are notoriously undetectable even among patients with pulmonary embolism so a negative finding may not mean a lack of clot. Nevertheless, because of this controversy, other mechanisms for PFO in stroke have been hypothesized including in-situ thrombosis or atrial tachyarrythmia but these remain unproven.

Atrial Septal Aneurysms and PFO

Atrial septal aneurysms (ASA) are caused by a redundancy of the intra-atrial septum and are found in approximately 1% to 2% of the population [10]. Similar to PFOs, several case-control studies have documented a relatively high prevalence of ASAs in patients with cryptogenic stroke. One study used TEE to document a 7.9% prevalence of ASAs in stroke patients compared with 2.2% in population-based controls. Case reports of thrombus formation on the membrane of ASAs have contributed to the hypothesis that these cardiac anomalies are thrombogenic and may lead to stroke.

ASA is more common among patients with PFOs. For example, a study of patients with cryptogenic stroke found an ASA incidence of 19.1% among patients with PFO compared to 3.2% among those without PFO [11]. Patients with cryptogenic stroke with both PFO and ASA may have higher stroke recurrence rates than PFO alone, although data on this are limited and inconclusive. One prospective study of these patients found a 15.2% four-year risk of recurrence compared with 2.3% among patients with PFO alone [10]. Others studies have not shown an increased recurrence rate associated with ASA and PFO [12].

Treatment of Cryptogenic Stroke Patients with PFOs

There are no data to support primary prevention of stroke among patients with PFO. For secondary prevention among cryptogenic stroke patients with PFO, medical, percutaneous, and surgical options are available [13]. Current data are insufficient to assess the relative merits of these options.

Medical therapy consists of aspirin, warfarin, or both. Current data are insufficient to recommend one treatment over the other or to advise a particular duration of therapy. In the minority of patients with documented thromboemoblism or hypercoaguable state, warfarin is recommended. In other patients, because the presumed pathophysiology of cryptogenic stroke with PFO is paradoxical embolism, some clinicians advise three months of warfarin followed by life-long aspirin. The data for this approach, however, are limited and the risk of bleeding on warfarin must be taken into account when tailoring therapy to an individual patient.

In patients with cryptogenic stroke and PFO in whom warfarin is contraindicated, mechanical closure may be considered. The traditional surgical approach to foraminal closure involves an open thoracotomy. There are limited data comparing surgical closure with medical therapy and all the available studies are hampered by small sample size, nonrandomized designs, inconsistent criteria for outcome assessment, or other factors that preclude definitive comparisons. Surgery also carries a significant risk of bleeding, infection, perioperative stroke, and other complications.

Percutenous PFO closure holds promise over surgical closure due to its less invasive nature. Two devices for percutaneous closure of PFOs have been approved by the FDA via the humanitarian device exemption: the Amplatzer PFO Occluder (AGA Medical Corp, Golden Valley, Minn) and the CardioSEAL Septal Occlusion System (NMT Medical Inc, Boston, Mass). Patients who have had a second cryptogenic stroke while on warfarin are candidates for device closure. Other patients wishing to undergo percutaneous closure before failing medical therapy should be referred to a tertiary center for enrollment in ongoing clinical trials.

Several observation studies have been published examining patients who undergo percutaneous PFO closure. Harms and colleagues [14] followed 237 patients undergoing PFO closure for the prevention of recurrent stroke. During a mean follow-up period of 1.5 years, there were 8 recurrent strokes (3.4%) and 7 patients died (3.0%), although only one death was secondary to recurrent stroke.

A meta-analysis by Landzberg and colleagues [15] evaluated 10 studies of transcatheter closure of PFO and 6 studies of medical therapy for presumed paradoxical embolism. The 1-year rate of recurrent neurologic thromboembolism with transcatheter intervention was 0% to 4.9%. Medical management was associated with a 1-year recurrence rate of 3.8% to 12.0%. The meta-analysis was limited, however, by uncontrolled data, non-standardized definitions, and baseline imbalances.

Migraines

Migraine headache is an episodic syndrome affecting approximately 8% to 13% of the adult population [16]. Patients with the disorder suffer from migraine attacks that are classified as occurring with or without aura depending on whether they have a prodrome of visual and neurologic symptoms. The underlying cellular mechanism of the disorder is incompletely understood, but substantial data suggests that triggers such as emotional stress or foods set off a neurologic cascade leading to an attack.

An association between migraine headaches and right to left cardiac shunts (most often PFOs) has been established. One study documented a rate of right to left shunts using TCD of 41% among patients with migraine with aura compared to 16% for healthy controls [17]. The relationship appears to be strongest among patients with migraine with aura. Several studies have found that patients with migraine without aura have right to left shunts at frequencies similar to healthy controls.

Because of this association, it has been hypothesized that paradoxical emboli through PFOs may be a trigger for migraine with aura. One study of patients undergoing PFO or ASD closure for hemodynamic reasons (stroke, large ASD, or decompression illness) documented a reduction in migraine frequency among 18 out of 21 patients [18]. Other small, retrospective studies have had similar findings [19-21].

These data led to the randomized Migraine Intervention with STARFLEX Technology (MIST) trial, the results of which were presented at the American College of Cardiology meeting in 2006 [22]. Conducted in the UK, the study randomized 147 patients with migraine who had failed medical therapy to PFO closure or sham procedure. For the primary endpoint, complete resolution of migraine symptoms at six months, there was no significant difference between groups. However, for the secondary endpoint, a 50% reduction in migraine symptoms, there was a 42% reduction in the device group compared to 23% for controls (p=0.038).

Several follow-up studies, including the MIST II trial (NMT), ESCAPE (St. Jude Medical), and PREMIUM (AGA MEDICAL) are currently underway to compare PFO closure to sham procedure among migraine patients in a randomized fashion.

Conclusion

Patent foramen ovale is a relatively common congenital cardiac anomaly present in a significant proportion of patients with cryptogenic stroke and migraine headache with aura. Patients with PFO and stroke have medical, surgical, and percutaneous options for management. Comparative data are needed to definitively establish the best therapy. PFO closure for migraine patients holds promise, although the technique is still under evaluation and not yet established as an effective therapy.

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