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The Relation of Migraine Headaches and Interatrial Shunts

Konstantinos G. Kappos, MD, Vassiliki Tsagou, MD, George Andrikopoulos, MD, Spyros Koulouris, MD, Stylianos Tzeis, MD, Chryssanthi Dasopoulou, MD, John Pyrros, MD, Athanasios Kranidis, MD, Antonis S. Manolis, MD

First Department of Cardiology, "Evagelismos" General Hospital of Athens, Athens, Greece

ABSTRACT

Foramen ovale plays a very important role in fetal circulation by bypassing the lungs and diverting circulation from the right to the left heart. With birth it is usually sealed; however, probe patent or incompletely sealed foramen ovale remains in approximately 25% of adults. Patent foramen ovale (PFO) acquires significance in various congenital heart diseases or other particular settings leading to a right to left shunt, and thus to paradoxical embolism. PFO has been associated with transient ischemic attacks or cryptogenic strokes and also a host of other problems, including migraine. The recognition of an association between migraine syndrome with aura and PFO appears to have come 'full circle' over the past two decades. Epidemiologic studies have suggested a notably increased PFO prevalence in persons suffering from migraine. The prevalence of migraine headache is higher in cryptogenic stroke patients with PFO than in the general population. Studies have suggested that closure of the PFO may reduce migrainous symptoms. The relation between this association and the recognition of migraine as a risk factor for ischemic stroke in the young is unclear, though right to left passage of circulating factors has been postulated in both syndromes. Despite case series and uncontrolled studies documenting beneficial effects of PFO closure in patients with migraine, particularly those also afflicted by cryptogenic stroke, the recommendation for PFO closure in patients with migraine alone will need to await the results of ongoing randomized trials.

ABBREVIATIONS:
ASA: atrial septal aneurysm
ASD: atrial septal defect
MRI: magnetic resonance imaging
PFO: patent foramen ovale
TEE: transesophageal echocardiography
c-TCD: contrast transcranial Doppler

KEY WORDS: *patent foramen ovale; atrial septal defect; migraine; percutaneous device closure*

INTRODUCTION

Migraine is classically defined as an episodic disturbance that manifests primarily as headache of various intensity and sensitivity to afferent stimuli, such as light (photophobia), sound (pnonophobia) and head movement [1]. Migraine headaches are described as a particular kind of headache characterized by a 'throbbing' or 'pounding' like pain. They are classically located on only one side of the head, but many people have migraines with pain on both sides of the head or 'all- over'. The pain of a migraine headache may last for hours or even days. Migraine affects approximately 12% of the population, 18% of women and 6% of men [2]. Migraines can be classified into two types: with aura and without aura. An aura is a neurological warning symptom that precedes the headache. Some patients with migraine headaches experience an 'aura' 10-30 minutes before the onset of the headache. Typical auras may be visual, seeing

Address for correspondence:
Konstantinos Kappos, MD
Ass. Director of Cardiology
A´ Department of Cardiology
Evagelismos General Hospital
Ypsilantou 45-47
Athens 10675, Greece
Tel: +30-210-7201458
E-mail: kostaskappos@hotmail.com

flashing lights, motor speed difficulty, weakness of an arm or leg, or sensory, tingling of the face or hands. Migraine headache with aura is a risk factor for the development of stroke. Many patients suffer from frequent and disabling episodes [3]. Patients with migraine are at increased risk for subclinical lesions in certain brain areas; magnetic resonance imaging (MRI) discloses silent infarct areas in the brain that are not depicted by computed tomography.

Migraine is co-morbid with numerous other illnesses, including psychiatric disorders such as depression, anxiety and bipolar disorder, epilepsy and stroke [4]. Strong pathophysiological links have been identified between migraine and these conditions. Various classes of drugs, most of them originally designed to fight epilepsy, high blood pressure, or some other disorder are used to treat people who have migraines. Daily preventive medications are available for people with frequent, debilitating headaches such as antidepressants, beta-blockers, calcium channel blockers, medicines also used to treat epilepsy and alternative treatments, vitamin B_2 and magnesium. Yet neurologists' expectations of success in quelling the headaches are generally modest. Consider topiramate, one drug now advertised as a migraine therapy [5]. It reduces the frequency of attacks by an average of about 40%, but it can cause forgetfulness, fatigue, nausea and skin sensations that have no apparent cause. That sort of trade off is typical of many migraine drugs [5].

INTERATRIAL SHUNTS

Historically, migraine has also been associated with heart disease, but this has proved difficult to confirm [4]. The relationship between migraine and cardiac right-to-left shunts is at best cloudy. Recent evidence has linked migraine to a common and usually benign defect of the heart, the patent foramen ovale (PFO). Interatrial shunts, particularly PFO and atrial septal defect (ASD), are present in about one quarter of patients. These shunts have been implicated in cryptogenic stroke and decompression illness as a result of paradoxical embolism.

Patent foramen ovale first described in 1564 by Leonadi Botali, and in 1877 Cohnheim described paradoxical embolism due to PFO. To understand PFO, we should have basic knowledge about developmental anatomy and physiological changes in circulation taking place after birth. A patent foramen ovale is a frequent remnant of embryological development with clinical importance in thromboembolism, paradoxical embolism, stroke, platypnea-orthodeoxia, decompression sickness and migraine headache [6,7]. At birth or shortly afterwards, the septum primum and the septum secundum usually fuse, closing the interatrial septum to the flow of blood. Ostium primum atrial septal defects occur when the septum primum fails to fuse with the endocardial cushion. Ostium secundum atrial septal defects occur when there is excess resorption of septum primum or inadequate development of septum secundum. A PFO persists when fusion of the septum primum with the septum secundum is inadequate [8]. We should remember that PFO is a result of the normal developmental process while ASD is the deficiency in the formation of atrial septum.

A PFO may allow right to left shunting under conditions of transient or permanent increase of right atrial pressure, such as during a Valsalva maneuver, coughing, sneezing, diving, or elevated heart pressures due to pulmonary hypertension or right heart failure. This may lead to conditions favoring paradoxical thromboembolism or shunting of chemical substances (such as serotonin) produced in the liver and ordinarily inactivated with their first pass through the lungs but now bypassing the pulmonary circulation through the interatrial shunt, all these mechanisms also proposed to partly explain the occurrence of migraine.

An atrial septal aneurysm (ASA), defined by echocardiography as a bulging in the region of the fossa ovalis, is associated with a PFO [7,9]. Septum membrane mobility is determined by the sum of excursions at rest, essentially the greatest leftward and rightward deflections of the septum primum with respect to a perpendicular line to the fossa ovalis plane into either the left or right atrium. The amount of septal excursion to meet this definition is arbitrary, although a sum of 15 mm or more has been suggested [10]. The presence of an ASA increases the risk of a PFO and more importantly that of a cryptogenic stroke or paradoxic embolism; if the association of a PFO with cryptogenic strokes has an odds ratio of ~5, this odds ratio for co-existing ASA climbs to 24. In addition to an ASA, other important risk factors for stroke or paradoxic embolism include the presence of other predisposing conditions, such as the presence of a Eustachian valve or Chiari's network in the right atrium, or underlying venous thrombosis, high right atrial pressure, or thrombophilia [11].

DIAGNOSIS OF INTERATRIAL COMMUNICATION

Most people with PFOs have no symptoms or signs of the defect. Blood traveling between the atrial chambers of the heart may cause symptoms such as fatigue, shortness of breath, atrial fibrillation, or other arrhythmias. Patients with large PFOs may have a heart murmur, either undetected or never evaluated. These may be referred to as benign, where in fact they were not. Unfortunately, PFOs and ASDs cannot be detected by physical exam only. *Transesophageal echocardiography* (TEE) is the preferred imaging study to confirm a PFO because it shows the most detail. We can see the gap in mid inter atrial septum or evidence of septal aneurysm with septal perforation. Contrast/ bubble echo is very helpful in

the diagnosis provided by appearance of micro bubbles in the left atrium within three cardiac cycles of their appearance in the right atrium which confirms the presence of a PFO. This can be made simpler by Valsalva maneuver during contrast echo. Also, *contrast transcranial Doppler* (c-TCD) is a very sensitive method to detect right to left shunts, the majority of which are due to PFO [12]. This method involves the use of an intravenous infusion of air and saline (agitated saline) or other contrast medium that produces a suspension of air bubbles or contrast particles with a diameter smaller than that of red blood cells, but unable to pass through the lung filter. This medium when injected into a forearm vein travels to the heart and, in case of a right-to-left shunt, it can be detected by transcranial sonography in the arterial tree at the level of middle cerebral artery, suggesting possibly a PFO, or other shunts [12]. The Valsalva maneuver enhances the sensitivity of the test. Recent studies comparing the transcranial sonography with the transesophageal Doppler indicate that the Valsalva maneuver shows an almost 100% sensitivity in transcranial sonography versus transesophageal and a specificity around 73% [12,13].

PFO TREATMENT

There is no consensus to treat asymptomatic PFO, but high risk PFO should be treated with antiplatelet and anticoagulant drugs. In the case of cryptogenic stroke and failed drug therapy, a percutaneous device closure is considered. A PFO can be closed without the need for surgery, using a small umbrella-like device and a percutaneous technique. The closure device is advanced into the left atrium through the PFO via a long sheath introduced via the femoral vein. This closure method is quite safe and effective. The procedure is performed with use of local anesthesia and usually takes about 30 minutes to complete. Patients typically go home the next day and are back to all their usual activities in a few days. Complications of the procedure may include thromboembolism, local bleeding, infection, device embolization, cardiac perforation and need for urgent surgery [14]. The closure devices are not affected by magnetic resonance imaging (MRI) or metal detectors as they are not metallic in nature.

RELATION OF PFO AND MIGRAINE

Recent studies have tied the occurrence of migraine to the presence of a PFO. A family history is present in up to 90% of patients with migraine [15]. Usually there is dominant inheritance with incomplete penetrance [15]. The incidence of interatrial communications, primarily PFOs, appears to be increased in patients with migraine, especially in patients who experience migraine with aura [16]. There is a 3.5-fold increased incidence of migraine headache in patients with a PFO or atrial septal defect (ASD) who are undergoing transcatheter closure of their interatrial communication. Transcatheter closure of PFO or ASD in patients with migraine leads to resolution of or significant improvement in severity of migraine in the majority of patients [16].

How could a PFO trigger migraine? It is thought that certain vasoactive substances in the body, like serotonin, that are normally taken up by the lungs, could pass unfiltered via a PFO to the blood destined for the brain, triggering a migraine in susceptible individuals. Why might this be? It is possible that blood without enough oxygen may trigger a migraine when it reaches the brain. The pain of migraine headache is thought to be caused by abnormal dilation of the brain blood vessels. The aura that precedes the headache in many people is thought to represent abnormal constriction of the blood vessels before they dilate. This constriction leads to a low blood flow in that area of the brain, and transient ischemia which causes the symptoms of aura. There are several factors that may trigger this hyperactivity of the blood vessels. Certain foods especially those containing substances that are 'vasoactive' like red wine, chocolate and aged cheese are often culprits. In women, hormonal changes at the time of menstruation may be a trigger. In some patients, the triggers are very clear. In other patients, the triggers are less well-defined, such as the role of peptide serotonin, which is neurologically active and does not usually circulate in blood heading from the heart to the brain. By closing the PFO, it is thought that these vasoactive substances are prevented from reaching the blood vessels in the head, removing a major migraine trigger. If true migraine or migraine-like symptoms are due to transient ischemic attacks (TIA) or paradoxic embolism is another query to be solved.

The link between migraine headaches and PFO was found only recently and by chance. The observation was made in patients with cryptogenic stroke and a PFO who also had migraine headaches. After these patients had their PFO closed to prevent recurrent strokes, many of them reported a dramatic reduction in migraine frequency. This link was looked at systematically by a number of investigators [5]. Schwerzmann and his colleagues at the University Inselspital Hospital in Bern, Switzerland, compared 93 patients suffering from migraine headaches with aura with 93 healthy controls [17]. They found that 47% of the migraine sufferers had a PFO. In contrast, only 17% of the controls had a PFO. These researchers found that patients afflicted by migraine were much more likely to have mid-sized or large PFOs, while those of the controls were generally small. This team of investigators found that migrainous headaches in patients who have had their PFOs closed were significantly improved or even eliminated.

Two groups of researchers from Belgium and Switzerland studied whether percutaneous closure would lead to fewer migraines. The Belgian group gave a questionnaire about

migraines to people after they had the PFO closed [18]. The Swiss group gave a questionnaire assessing the headache frequency and characteristics for the year before and after the PFO closure [19]. There was no appreciable effect on the non- migraine headache patients. In both studies, the PFO closure was done for cryptogenic stroke. The frequency of migraine was decreased in both studies after PFO closure. Only the Swiss study evaluated both migraine and non-migraine headaches. These studies add to the growing body of evidence that there is an association between a PFO and migraine. First, the number of people who had migraine with aura in both studies was higher than in the general population. Second, PFO closure was associated with reduction of migraine symptoms in patients having migraine both with and without aura. Third, in the second study, non migraine headaches were not affected by PFO closure. These studies are important in that they provide a clue to a potentially correctable trigger of migraine. However, they do not support PFO closure as a treatment for migraine because of two major limitations. The studies were retrospective, they asked patients for information about their headaches that occurred in the past; and they studied only stroke patients. To get better results, a study is needed that evaluates otherwise healthy migraine patients and collects information in real time, prospectively, and treatment is allocated in a randomized manner.

The prevalence of migraine was very high in patients with stroke or decompression sickness who had PFOs. A series of five studies with those patients evaluated or treated for PFO / right- to- left shunts has demonstrated an overall prevalence of migraine of 22-57%, migraine with aura of 18-43% and migraine without aura of 14-21% [18-22]. Studies have also shown that the prevalence of migraine is higher with larger shunts [23].

Another study determined the effects of transcatheter PFO closure on migraine frequency in patients with paradoxical cerebral embolism [5]. A cohort of 162 patients with paradoxical cerebral embolism underwent transcatheter PFO closure for prevention of recurrent cryptogenic stroke or transient ischemic attacks. A one-year retrospective analysis of migraine symptoms before and after PFO closure was performed. Migraine symptoms were completely relieved in 56%, significantly reduced in 14% of patients and 30% reported minimal or no relief of migraine. The conclusion was that in patients with paradoxical cerebral embolism, migraine headaches are more frequent than in the general population and transcatheter closure of the PFO results in complete resolution or marked reduction in the frequency of migraine headache. Although many migraine sufferers are eager for any procedure that could offer them potential relief from the debilitating attack, controlled clinical trials are needed before recommending PFO closure procedures as a possible migraine treatment. There are migraine sufferers who do not have interatrial shunts, and people with PFOs and ASDs who do not suffer from migraine; so the link seen in this study, even if confirmed, does not explain all migraines.

Overall there are at least seven studies that show that percutaneous PFO closure cures migraine or offers significant improvement [25]. However, despite the promising findings and advances, most researchers do not yet consider that PFO closure is ready for prime-time use in treating migraines, as these studies thus far have not been randomized and properly designed to rule out alternative explanations for patients' improvement. Researchers also do not know whether these findings apply to patients with migraines but without strokes or other problems that have been previously associated with a PFO. It has been suggested that the relief of headaches might be a response to clopidogrel which these patients usually receive and this would be in keeping with the role of platelets as a potentially major etiologic factor. Further studies are clearly needed to investigate the role of clopidogrel or of the combination of clopidogrel and aspirin therapy in these settings [26]. Nevertheless, some data indicate that the relief of headaches persists even after discontinuation of the antithrombotic therapy usually slated at 5-6 months after the device implant procedure.

To date no isolated data have been published about the relationship between migraine and the presence of an atrial septal defect. Although an ASD is mainly characterized by a left to right shunt and volume overload of the right heart, a small right to left shunt may occur during Valsalva or exercise. Theoretically, this right to left shunt could also permit the lung filter to be bypassed. Indeed, there is a high prevalence of migraine in patients with an unclosed secundum type ASD (up to 30%) [27]. This seems to be higher than in the general population, but lower than in patients with PFO [2].

ONGOING RANDOMIZED STUDIES

All PFO closure studies so far have been non-randomized, fairly small and observational. To establish a true benefit from PFO closure, large randomized controlled trials are required. Such trials are currently ongoing. The preliminary results of the first such study, the 'MIST' (Migraine Intervention with STARFlex Technology) trial, which was conducted in the UK, were just presented during the 2006 American College of Cardiology annual meeting in Atlanta [23,24]. These results confirmed previous studies showing that medium-to-large cardiac shunts, mostly PFOs are common in patients having migraine with aura. The prevalence of small shunts was little different from that seen in the general population, but the prevalence of medium-to-large PFOs was about 6-fold greater than expected. The MIST trial randomized 147 patients to PFO closure with the STARFlex device (n=74) or to a sham procedure (control group; n=73). Patients were followed for 6 months evaluating migraine frequency and severity; patients

were treated with aspirin and clopidogrel for the first 3 months. The study showed that there was no difference between the two groups in the primary endpoint of complete cessation of migraines (only 3 patients in each group had elimination of migraine). However, headache reduction by at least 50% occurred more frequently in the PFO closure group (42% vs 23%, p=0.038).

More randomized, double-blind, placebo-controlled studies currently recruiting patients with migraine and a PFO include the MIST II trial conducted in the US (550 patients), the "ESCAPE" ('Effect of Septal Closure of Atrial PFO on Events of Migraine with Premere') trial, also conducted in the US, the FORMAT ("Patent Foramen Ovale Closure to Reduce Migraine Attacks") trial (Holland & Belgium), and the PREMIUM ("Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction In Subjects with Migraine & PFO Using the Amplatzer PFO Occluder Compared to Medical Management") trial (USA) [27].

CONCLUSION

Despite the promising findings and advances, most researchers do not think that PFO closure is ready for prime time use in treating migraines. They harbor lingering doubts because the studies thus far were not designed to rule out alternative explanations for the volunteers' improvements. Researchers also do not know whether the findings apply to people with migraines but without strokes or other problems that have been previously associated with a PFO. As indicated above, several randomized clinical trials are currently ongoing, and it is expected that within two years, we could have conclusive evidence whether PFO closure works against migraines. If these studies confirm the initial findings, millions of people could consider closure of PFOs as a treatment option for migraines.

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