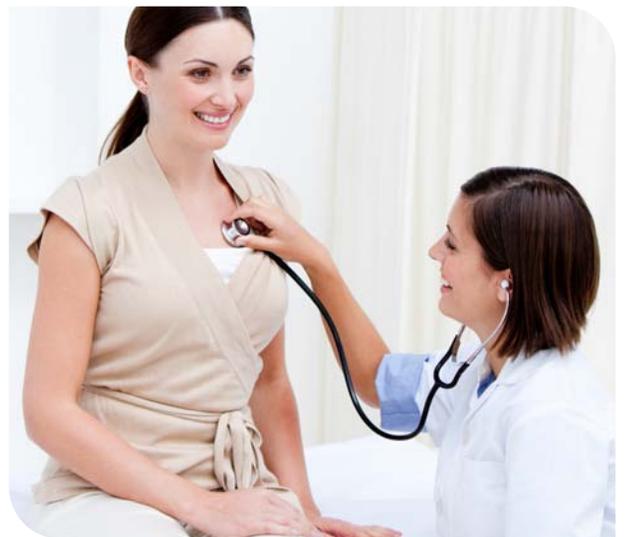




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A Guide For Patients: Patent Foramen Ovale (PFO)

Glossary of Terms

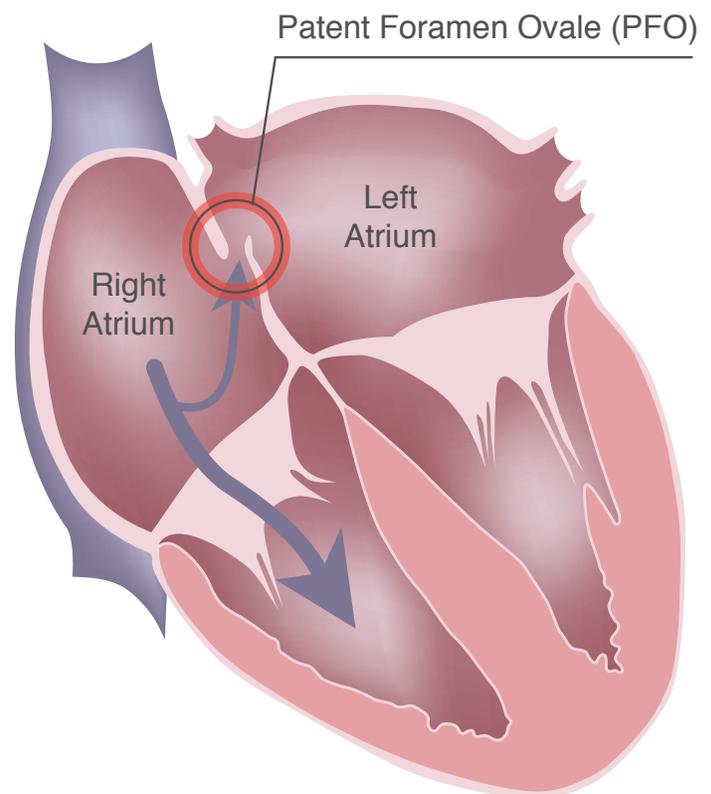
Here are some common terms related to PFO.

- » **ASA** - Atrial septal aneurysm, an abnormally enlarged, bulging and mobile atrial septum (a wall in the heart separating the 2 upper chambers). An ASA associated with a PFO is thought to produce an anatomical condition that is more likely to cause clinical problems.
- » **ASD** - Atrial septal defect, a form of congenital heart defect that enables blood flow between the left and right atria via the interatrial septum. ASD's do not have a flap of tissue over the opening whereas PFO's have a flap of tissue.
- » **Aura** - unusual visual, olfactory, or other sensory experiences accompanying severe migraine headaches
- » **Catheter** - Thin flexible tube inserted in the body from a leg, arm, or neck vein or artery and used for delivering therapies such as medications, electrical energy, or implanting medical devices, like a PFO closure device.
- » **Occluder** - Another name of a non-surgically implanted device to occlude a PFO or ASD.
- » **"Off-Label"** - The use of a medication or medical device for an unapproved indication as defined and governed by the US Food and Drug Administration (FDA)
- » **PFO** - Patent foramen ovale (PFO) is a small opening covered by a flap of tissue in the wall of the heart that separates the two upper chambers or atria. Since they are so common and are generally not considered a problem, i.e. they are incidental, PFO's are not considered an abnormal structure but a remnant of the way the heart is constructed in all people when they are in their mother's wombs. Most PFO's fuse shut shortly after birth.
- » **Shunt** - A condition whereby blood from the right and left sides of the heart mix inappropriately.
- » **Sleep apnea** - A medical condition including repeated abnormal pauses in breathing. Obstructive sleep apnea (OSA) includes the occurrence of obstruction of the airway to the lungs. The presence of a PFO may worsen this condition.
- » **TIA** - Transient ischemic attack, often referred to as a "mini-stroke" is an episode in which a person has stroke-like symptoms but they are transient, i.e. last less than 24 hours, and are not associated with brain damage, i.e. are not a stroke or CVA (cerebro-vascular accident).
- » **Valsalva maneuver**: To transiently open a PFO, a person is asked to perform a Valsalva maneuver that consists of taking in a large breath, holding it, bearing down by contracting muscles typically used during child birth or a bowel movement, and then releasing it. During the release phase of a well-performed Valsalva maneuver, the pressure on the right atrial side of a PFO is greater than the left atrial side. The PFO flap opens, and injected micro-bubbles will immediately appear in the left atrium from shunting through the open PFO.

Fast Facts

- » A patent foramen ovale (PFO) is an opening covered by a flap of tissue in the wall of the heart that separates the two upper chambers or atria.
- » PFOs are very common, more than 20% of all humans have one.
- » PFO's are found in up to 55% of young (<60 yo) patients with stroke of unknown cause and 48% of patients suffering from migraine with aura
- » Unless a patient has symptoms related to a PFO or other associated heart defects, there's no need to seek treatment
- » Most PFO's in healthy people are incidental findings but in some patients the PFO is related to a problem
- » The most common problem associated with a PFO has been a stroke or a temporary neurological event and/or severe migraine headaches
- » A PFO can allow deoxygenated blood (venous blood with a low amount of oxygen) or blood clots to pass from the right side of the heart to the left and travel to the brain, preventing blood flow to that part of the brain or lowering oxygen levels for the whole body
- » PFO treatment for patients with strokes of unknown cause typically involves extended use of blood-thinning medication such as aspirin, or prescription drugs, or physically closing the PFO using one of several devices
- » Catheter-based (non-surgically) implanted PFO closure devices are still pending official approval by the US Food and Drug Administration
- » Several clinical trials are underway for PFO patients who have suffered a stroke or who suffer from migraines to assess the role of device closure of PFO

For more information, visit www.pforesearch.org.



What is a PFO?

Patent foramen ovale (PFO) is a small opening with an overlying flap in the wall of the heart that separates the two upper chambers or atria. The wall between the upper chambers of the heart, the atria, consists of two overlapping layers of tissues, the septum primum and septum secundum. When the two layers fail to normally fuse together shortly after birth, the flap opening is called a PFO, which is a Latin derived medical term - Patent (to lie open) Foramen (window) Ovale (oval in shape).

Who Has a PFO?

PFO's are fairly common – they occur in approximately 20% of the adult population. Unless you suffer from severe migraine headaches or have had a neurological event such as a stroke, chances are you wouldn't need to seek medical treatment for your PFO. In fact, since PFO's are so common, the detection of a PFO in an adult is usually incidental, i.e. has nothing to do with causing any problem.

PFO's do not cause chest pain, heart palpitations, or heart failure. PFO's typically do not disrupt heart function and people are able to exercise and carry out all activities normally. However, some people with PFOs can be at an elevated risk of stroke or suffer other symptoms due to a significant drop in oxygen levels.

Why Treat a PFO?

A PFO and Atrial Septal Defects (ASD) are often referred to as a “hole in the heart.” The PFO's flap-like valve enables shunting – the abnormal mixture of blood between the right and left sides of the heart. If the PFO allows right-to-left shunting, oxygen-deprived blood can carry harmful substances to the brain. These substances include small blood clots, chemicals that may trigger migraine, or nitrogen bubbles that form when coming up from deep-sea dives. Blood clots that cross a PFO and travel directly to the brain, lodge in an artery and can limit blood flow to a part of the brain causing a stroke or transient ischemic attack (TIA).

PFO patients often have one or more of the following symptoms:

- » Cryptogenic (unknown cause) stroke
- » Migraine headache
- » Hypoxemia (low blood oxygen)
- » Decompression illness in divers
- » High altitude sickness, specifically pulmonary edema with worse than expected low oxygen blood levels
- » Sleep apnea with worse than expected low oxygen blood levels
- » PFO and Stroke

Stroke is currently the leading cause of disability and is projected to pass heart attacks as the leading cause of mortality worldwide. Approximately 40% of all strokes are classified as cryptogenic – meaning that the cause is unknown. While PFO's are present in approximately 20% of the population, between 40% to 50% of patients younger than age 55 with cryptogenic stroke have PFO.

PFO and Migraine

Migraine headache is a public health problem of enormous scope that has an impact on both the individual sufferer and on society. In the United States, three large population studies have established the prevalence of migraine at 18% in women and 6% in men.

The potential relationship between PFO and Migraine / Aura: It has been observed by different centers in Europe and the United States, that people who complained of migraine headaches and then had their PFO closed (usually due to a stroke) claimed that their headaches were completely alleviated in 60% of the patients and in an additional 15% of patients the frequency of headaches was reduced by one half. This has led to the theory that a PFO may permit certain chemicals that ordinarily would be metabolized as the blood passes from the right side of the heart through the pulmonary circulation, to bypass the lungs and permit blood from the veins to directly enter the brain. There may be some chemical or perhaps low oxygen itself, which then could trigger a migraine in susceptible people. This theory is currently being tested in a randomized clinical trial in the United States called the PREMIUM trial.

How PFO are Diagnosed

PFO's are not detected on a physical exam, an electrocardiogram, a stress test, or a chest x-ray. An echocardiogram visualizes the heart and shows the passage of micro-bubbles that are injected into an arm vein and then pass from the right atrium directly into the left atrium of the heart through the PFO. PFO's are often in a closed position and it may take certain “provocative maneuvers” to cause the PFO to open and be detected. Holding one's breath, straining of chest and stomach muscles, and then releasing the straining and breathing is a common “provocative maneuver” called the Valsalva maneuver, named after an Italian physician from the 17th century.

The echocardiogram cannot only reveal the presence (or absence) of a PFO, it can also approximate its size and shape. It can also reveal the presence of other related defects such as an atrial septal aneurysm (ASA), the flap of tissue that bulges in a balloon-like shape.

Treatment Options

Medical treatment

Patients who have had a stroke or other neurological event are often given blood thinning medication, such as aspirin, Plavix (clopidogrel), or Coumadin (warfarin) to minimize the risk of recurring stroke.

Open heart surgery

It is extremely rare to consider open-heart surgery to close a PFO since it can be closed with less risk and less trauma to the body by a procedure involving catheter delivery of a PFO closure device. When open heart surgery is needed, the PFO is closed by the placement of sutures that seal the flap covering the PFO. In some cases the surgeon may remove the tissue and replace it with a piece of the patient's pericardium or a medical cloth patch.

Robotic surgery

Robotic surgery is a form of open heart surgery that has multiple small incisions in the chest rather than one large incision and uses a robotic device to hold and manipulate small surgical instruments to repair the heart using video camera guidance.

PFO closure using an implanted medical device

Rather than open-heart surgery, a PFO closure procedure does not involve incisions in the chest, the heart being stopped, or the prolonged recovery needed after open-heart surgery. Rather the heart is reached via the insertion of catheters typically in a leg vein, maneuvered to the heart, and then used to insert or implant a medical device. The heart remains beating and the procedure is often done with the patient lightly sedated and using local anesthesia over the leg vein.

PFO closure involves the insertion of a septal occluder, or cardiac implant in the PFO to reduce or eliminate shunting. The device is designed specifically for septal defects. There are several devices that have been developed. Most devices incorporate some form of metal that acts as a spring to form 2 discs on opposite sides of the atrial wall. The device itself may close the PFO, or it approximates the flap of the PFO and the wall of the atrium so that it forms a substrate onto which, over time, the body's natural tissue grows, thereby closing the hole.

During the procedure, ultrasound imaging is used to identify the correct size, fit and placement of the PFO closure device. The device is then inserted through the catheter and moved to the correct location. Once in place, each side of the device opens in parallel, on each side of the PFO and then closes to hold the PFO shut. Catheter-based PFO closure is a simple procedure that typically takes 1 hour to complete. The procedure is often done on an out-patient basis, or with a brief hospital stay.

PFO closure offers a very high success rate and low risk of subsequent complications. However, no medical procedure is free of complications. Risks of PFO closure include bleeding from the vein in the leg, bleeding from the heart, arrhythmias, an increase in headaches, or chest pain. Depending on the device, these symptoms can be so severe that the patient may want the device removed. Once scar tissue has formed over the device, the only way to remove it is with open-heart surgery. Hopefully, the results of current randomized clinical trials will determine whether the benefits of PFO closure outweigh the potential risks of the devices. Recovery following PFO closure typically involves restriction from vigorous physical activity for several weeks following the procedure.

Clinical Trials

Clinical trials are vital toward the advancement of science for PFO treatment. Some trials compare the treatment of PFO via device-based closure to medical management for migraine sufferers. Other trials compare closure of PFO versus medical therapy to reduce clot formation to prevent recurrent stroke in stroke victims.

The reality is that most clinical trials are expensive to perform and must be sponsored, must have high scientific standards, and often take years to complete. Several PFO closure trials have struggled to finish due to slow enrollment. Many patients are merely unwilling to take part in randomized trials that assign patients to treatment with the traditional therapy versus the new therapy. Some patients never hear about clinical trials. Many trials are designed such that only a small percentage of patients with the problem are eligible to be enrolled. Some patients undergo PFO closure on an off-label basis. Some trials are simply difficult to perform for many potential research sites due to the many regulatory and administrative hurdles that exist.

Examples of ongoing clinical trials related to PFO are:

- » (CAMP) Study Comorbidities Associated with Migraine and PFO
- » Premium Trial - PFO/Migraine
- » REDUCE Trial - PFO/TIA or Stroke
- » RESPECT Trial - PFO/Stroke
- » Divers with PFO

The US Food and Drug Administration (FDA) currently promotes the enrollment of patients into clinical trials in order to ensure the safety and effectiveness of PFO Closure procedures. Some patents can obtain closure on an "off-label" basis, however. In Europe, different regulatory standards exist, and closure is more generally accepted. Estimates of the number of PFO closures currently being performed in clinical practice using both approved devices in Europe and off-label devices in the United States are in the thousands to tens of thousands worldwide. The results from ongoing, properly controlled clinical trials of catheter PFO closure for a variety of clinical syndromes are anxiously awaited in order to guide and inform clinical practice.

Costs and Insurance

Medical care in general is expensive and clinical trials are often costly. Who pays for the evaluation and treatment of PFO related problems is an important issue. In the US the issue is complex because medical insurance comes in many forms and there are a substantial proportion of patients without medical insurance. PFO closure procedure can cost between \$30,000 and \$60,000.

Clinical trials often cover costs of the experimental treatment but expect the routine care of the patient to be covered by the patient's insurance and the patient.

Off-label use of medical devices, as well as drugs, is usually covered by insurance companies since the diversity of patients and their medical conditions often require physicians to individualize therapy for them. Off-label closure of PFO's has occasionally resulted in insurance company denials to cover the procedure because there is no FDA approved PFO device in the US and the treatment in general is considered experimental. There are arguments and counter arguments, but the bottom line is that patients must be aware of their insurance companies policies and be prepared for needing to appeal their case if denial occurs.



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