Pro: An Incidental PFO Should Be Repaired When Discovered During Planned OPCAB Surgery

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PFO--WHAT IS IT?

The foramen ovale is bordered by the septum secundum (limbus of the fossa ovalis) and the septum primum, which serves as a valve within the fossa ovalis, and allows blood to flow from the right atrium to the left atrium. Normally, the foramen ovale closes functionally after birth, when lung expansion and initiation of the pulmonary circulation reverses the pressure gradient between the atra. A PFO develops when the atrial septum fails to seal with fibrous adhesions after birth (normally this fusion is complete by 1-2 years of age). This allows a potential shunt to be present, although the PFO generally remains closed by the normally higher left atrial pressure. A PFO occurs in more than 25% of the U.S. population.

PFO--HOW COMMON IS IT?

The reported incidence of PFO is: 25% of normal healthy adults; 27.3% of autopsy specimens; 34.3% in first 3 decades of life; 25.4% in the 4th-8th decades; and 20.2% in the 9th-10th decades. PFO prevalence decreases with age in a linear fashion. This has led pathologists to interpret this as meaning there is late closure of the PFO. Conversely, there may be a shortened longevity associated with PFO, thereby making the incidence lower in the elderly. The size of a PFO increases with age, secondary to stretching of the fossa ovalis (causing greater separation of the ostium secundum).

PFO--WHY DO WE CARE?

PFO can lead to two major adverse events: shunting of deoxygenated blood into the systemic circulation, and paradoxical embolism of air or thrombus/fatty material. PFO has been linked to cryptogenic strokes. Over 40% of all ischemic strokes have no well documented cause and are considered cryptogenic. Approximately 50% of patients with cryptogenic stroke have a PFO. This is especially relevant in patients < 55 years of age. Cases of hypoxemia in patients with a PFO or small ASD have been reported in the presence of normal right atrial pressures and responded to percutaneous closure.

DIAGNOSIS OF PFO

Contrast TEE is considered to be the modality of choice for diagnosing PFO. A PFO is confirmed if microbubbles appear in the left atrium within 3 cycles of complete opacification of the right atrium (to differentiate from extracardiac/pulmonary shunts). Color flow Doppler using a low pulse repetition frequency provides comparable and perhaps greater accuracy because it is not influenced by the presence of a Eustachian valve. In the presence of a prominent Eustachian valve, blood injected from the lower extremities (via the IVC) allows more passage of bubbles across a PFO compared to blood injected via an upper extremity I.V. (i.e. improved sensitivity and specificity of the bubble test).

Under normal circumstances, left atrial pressure is greater than right atrial pressure. There is a brief pressure reversal in early ventricular systole. During the release of a Valsalva maneuver or during coughing, there is increased venous return to the heart, leading to transient elevation of right atrial pressure. Coughing or inducing a Valsalva maneuver can increase the detection of a PFO that is not seen without such provocation.
MORPHOLOGY OF PFO

PFO is characterized by: size (maximum separation of septum primum and septum secundum), presence of atrial septal aneurysm (ASA), severity of shunting by contrast injection (mild, 3-9 microbubbles; moderate 10-30 microbubbles; severe > 30 microbubbles), prominence of Eustachian valve, presence of Chiari network; tunnel length (maximum overlap of septum primum and septum secundum).

It has been shown that patients with CVAs had larger PFOs, longer tunnels, and a greater incidence of ASA.

ATRIAL SEPTAL ANEURYSM

An atrial septal aneurysm (ASA) is made up of thin tissue in the region of the fossa ovalis that moves rhythmically with the cardiac and respiratory cycles, protruding into and out of the atrial cavities. It is frequently seen in association with a PFO. Paradoxical embolism is believed to be the likely mechanism of embolic events in patients with ASA, although other potential mechanisms of cardioembolism have been postulated, including thrombus formation within the ASA, supraventricular arrhythmias, and associated mitral valve prolapse.

ROLE OF THE EUSTACHIAN VALVE

The Eustachian valve is the embryological remnant of the fetal sinus venosus valve. It can be seen as an echo dense ridge-like or undulating structure at the junction of the IVC and right atrium. It is present in up to 70% of patients who have a PFO. Persistence of the Eustachian valve may prevent spontaneous closure of a PFO after birth by directing blood from the IVC to the interatrial septum. Eustachian valve thrombosis has been described, and in the presence of a PFO can lead to paradoxical embolization.

ANATOMY VS. PATHOPHYSIOLOGY

Both anatomic and pathophysiologic variables contribute to stroke risk in patients with a PFO. Interatrial pressure gradients play an important role in the development of stroke. The mechanisms behind the etiology of cryptogenic stroke in patients with PFO are speculative at best. Anecdotal observation of large thrombi migrating across a PFO has led to the assumption that embolization is the primary mechanism. Others have suggested that smaller embolic material can form in situ within a PFO. The “tunnel” of the PFO would thereby provide a procoagulant environment where there is stagnation.

EPIDEMIOLOGY OF STROKE

Stroke is the third leading cause of death in developed countries and a primary cause of long-term disability and hospitalization. Eighty-eight percent of the 700,000 strokes that occur annually in the U.S. are of ischemic etiology, and in more than 40% of cases of ischemic stroke, no clear source could be identified (i.e. cryptogenic). There is a 40-56% incidence of PFO in patients with cryptogenic stroke. This is especially true in patients less than 55 years old. When you add up the numbers, 98,000-139,000 strokes could theoretically be due to PFO each year. A PFO can allow microemboli to traverse into the left heart and enter the cerebral circulation. Deep vein thrombosis and clotting deficiencies can potentially increase this risk.

Government statistics show that the mean lifetime cost of ischemic stroke is $140,000 per patient. In 2007, stroke-related costs were expected to reach $62.7 billion dollars nationally.

DEEP VEIN THROMBOSIS

The incidence of deep vein thrombosis (DVT) in the general population is close to 1:5,000, and increases with age. In some patients there is an underlying hypercoagulable disorder (e.g. antiphospholipid

In the presence of a PFO > 4 mm, patients with pulmonary embolism have a 10x risk of death and 5x risk of systemic embolism compared to patients without a PFO.

PRECIPITATING FACTORS FOR SHUNTING WITH PFO

Conditions that lead to elevated right atrial pressure increase the risk of shunting and hypoxemia in the presence of a PFO. Likewise, conditions that lower left atrial pressure can increase right-to-left shunting across a PFO (this is particularly relevant in patients undergoing placement of a left ventricular assist device). Conditions that alter or distort the normal anatomical relationships within the heart can result in increased right-to-left shunting in the presence of a PFO. Finally, numerous conditions are associated with elevated right atrial pressure: pulmonary embolism, adult respiratory distress syndrome (ARDS), severe tricuspid regurgitation, hypoxic pulmonary vasoconstriction, right ventricular infarction, poor right ventricular preservation during cardiopulmonary bypass, right-sided tamponade, severe COPD, obstructive sleep apnea (OSA), Pickwickian syndrome, asthma, PEEP, and mechanical ventilation.

It has been shown in one study that patients with severe COPD have an increased prevalence of PFO, and that approximately 50% of patients with severe COPD and PFO show significant oxygen desaturation during a Valsalva maneuver.

During nocturnal apneic periods, patients with OSA develop transient elevations of right-sided pressures.

PEEP and the inspiratory phase of mechanical ventilation can lead to an increase in pulmonary vascular resistance, and lead to a reversal of normal interatrial pressure gradients.

During sitting craniotomy for posterior fossa surgery, it is not uncommon for air to be entrained into the venous system. Venous air embolism is a well recognized phenomenon with these types of procedures, and can result in systemic air embolization in the presence of a PFO.

Long bone fractures and total joint arthroplasty can lead to paradoxical fat embolism in the presence of a PFO.

Deep sea divers with a PFO are at greater risk for decompression sickness. During decompression, nitrogen bubbles develop and become trapped in the pulmonary microvasculature, leading to an increase in pulmonary artery pressure. This finding, along with a Valsalva maneuver, that is often done to equalize middle ear pressure, can lead to gas embolization across the PFO. PFO can worsen hypoxemia in scuba divers at great depths.

At high altitudes, PFO can lead to hypoxia secondary to hypoxic pulmonary vasoconstriction, leading to elevated pulmonary artery pressures. Hypobaric decompression sickness has been described in high altitude aviators and astronauts during extravehicular activity.

Platypnea-orthodeoxia syndrome is a rare condition that manifests as dyspnea (platypnea) and arterial desaturation (orthodeoxia) occurring in the upright position, and relieved by assuming a recumbent position. It was originally described in 1949, and has been associated with pneumonectomy, lobectomy, COPD, cirrhosis, and ascending aortic aneurysm. Most cases have been described in patients with previously asymptomatic interatrial shunts who underwent pneumonectomy. In particular, right pneumonectomy can alter venous return to the right heart by distorting the relationship of the IVC to the fossa ovalis, such that IVC blood is preferentially directed towards a PFO.

During migraine attacks, there is hyperaggregation of platelets. It has been suggested that microembolization in the vertebrobasilar territory across a PFO causes migraine with aura in some instances.
PFO may also be associated with arterial vascular occlusion to the retina and optic nerve.

Decreased left ventricular afterload with normal right atrial pressure has been described as leading to right-to-left interatrial shunting.

The concept of atrial vulnerability, which is based on effective refractory periods, atrial conduction time, and inducible atrial fibrillation, is apparently frequent in patients with cryptogenic stroke (PFO, ASA, or both). PFO and ASA have also been associated with an increased incidence of postoperative atrial fibrillation following CABG.

**SO, WHAT IF YOU HAVE A PFO AND…**

Do a Valsalva maneuver?
Require PEEP during postoperative mechanical ventilation?
Have a THA complicated by fat embolism?
Sustain long bone fractures?
Undergo sitting craniotomy?
Have obstructive sleep apnea?
Have severe COPD?
Have transient global amnesia?
Develop a pulmonary embolism?
Scuba Dive?
Work in a compressed air tunnel?
Have a chronic cough?
Are a high altitude aviator? (HPV occurs at high altitude)
Are an astronaut engaging in extravehicular activity?
Use birth control pills and develop ATIII deficiency?
Develop tamponade following OPCAB?

**TREATMENT OPTIONS FOR PFO**

There are four: do nothing, anticoagulation with warfarin, antiplatelet therapy, and PFO closure (surgical or percutaneous device)

**WHAT WE DO KNOW ABOUT PFO CLOSURE**

Between 1998 and 2004 the surgical volume for PFO closure has remained relatively stable, while percutaneous closure has increased more than 50-fold. Antiplatelet and anticoagulant therapy (i.e. medical management) have a significant failure rate for the prevention of recurrent stroke/TIA in patients with a PFO.

In cryptogenic stroke patients, PFO closure does not guarantee freedom from recurrent neurological events in the future. Furthermore, other stroke etiologies may come into play. One has to keep in mind, however, that published studies lack consistency. Things to consider when reviewing and interpreting this literature include:


Other risk factors for stroke: hypercoagulable state?

How often do we ask our patients about specific risk factors, such as their interest in scuba diving, or whether their migraines are associated with aura?
CABG AND THE INCIDENTAL FINDING OF A PFO

Because intraoperative TEE is frequently used in cardiothoracic surgery (routinely in many institutions), it goes without saying that incidental PFOs are being detected with greater frequency. The question that remains to be answered is whether or not an incidental PFO should be closed. For open cardiac procedures, PFO closure adds little to the operating time and does not alter cannulation strategy. Greater consideration must be given when an off-pump strategy or a non-intracardiac operation (i.e. CABG, AVR) should be altered to address a PFO. To date, there are no randomized trials that help to answer this question, so the question that must be addressed is whether the benefit of closing an incidental PFO is greater than the risk of leaving it alone. The other point that needs to be questioned is the rationale behind off-pump versus on-pump CABG. Reasons for avoidance of cardiopulmonary bypass include patient characteristics (co-morbidity, aortic atherosclerosis precluding aortic manipulation) and surgeon preference. By itself, PFO closure is a relatively low risk procedure, and published studies report no mortality and little morbidity.

There have been several case reports describing patients with PFO who underwent uncomplicated on-pump CABG that was complicated by worsening of right-to-left shunting in the postoperative period. Clearly, any factor leading to worsening right ventricular function (infarction, pulmonary embolism, poor myocardial preservation) can lead to an increase in right atrial pressure and increased shunting with hypoxemia.

During off-pump CABG, cardiac manipulation/elevation can potentially lead to right-to-left shunting and hypoxemia, which can be even more detrimental when the wide hemodynamic disturbances that can occur are taken into consideration. A case has been reported where a patient underwent OPCAB (without intraoperative TEE) and had to return to the OR for PFO closure for refractory hypoxemia.

We really don’t know the impact of a PFO on postoperative outcomes. Is the risk of placing a patient on cardiopulmonary bypass for a short interval greater or less than the risk of developing a stroke in the short or long term?

Things to consider when deciding on whether to change operative strategies from off-pump to on-pump in order close a PFO include presence of:

- Shunting without provocative maneuvers
- History of TIA/stroke of unknown etiology
- Atrial septal aneurysm
- Elevated right-sided pressures
- Pulmonary hypertension
- Presence of a prominent Eustachian valve
- Obstructive sleep apnea
- Hypercoagulable state
- Severe right ventricular dysfunction
- History of migraine with aura
- DVT or PE history
- Activities associated with shunting from a PFO (scuba diving, flying, high altitude climbing)

We don’t know the actual incidence of perioperative PFO-related morbidity. It can also be difficult to differentiate between individual causes of stroke and hypoxemia.

A large body of equivocal information comes from case reports, case series, and retrospective or observational analyses. Until properly conducted randomized prospective studies are undertaken, the answer to the question “What should be done when an incidental PFO is detected at the time of cardiac operation?” will elude us. The escalating number of percutaneous device closures for PFO may hinder matters further, because of unwillingness to randomize patients to a non-treatment group.
REFERENCES

1. American Heart Association Heart Disease and Stroke Statistics—2006 Update (http://www.americanheart.org/presenter)