REVIEW

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Patent foramen ovale and cryptogenic stroke: still needs a complete study

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ABSTRACT

Patent foramen ovale (PFO) is a residual of normal fetal anatomy. More than half of babies will develop PFO at six months of age. PFO may cause shunts from right to left, and the possibility for shunting from venous thromboembolism into the arterial circulation. Since then, many idiopathic stroke studies have been conducted, in which PFOs are often found. PFO does not require follow-up treatment in infants and children, and venous thromboembolism should also be evaluated for idiopathic stroke in young patients to assess the trend of thromboembolism associated with PFO, which affects morbidity and mortality. The decision to treat depends on the presence, size and presence of complications.

Keywords: patent foramen ovale, idiopathic strokes, management, morbidity, mortality.
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INTRODUCTION

The foramen ovale (FO) is a normal part of fetal circulation. Oxygen-rich blood flows from placenta to fetal arterial circulation via FO. Postnatally, the fusion between two embryonic structures of the atrial septum, namely the primum and secundum septum, causes a closure of the foramen ovale. The partial coalition between primum and secundum septum will generate a Patent Foramen Ovale (PFO).[1,2]

Stroke is one of the stronger predictors of death and morbidity globally. After eliminating all potential causes, around 20% to 30% of all ischemic strokes still do not have any identifiable reason; hence, it is known as cryptogenic stroke.[3] PFO is estimated to be one of the etiologies of cryptogenic stroke.[4] Between 40% to 50% of patients with idiopathic stroke was with PFO.[2]

PFO is a potential pathway for embolic transit of platelet aggregation, thrombus, gas bubbles, or other particulate matters from the systemic venous circulation to the cerebral blood vessels. Also, the PFO can potentially be an origin for embolic thrombus formation in situ.[5] The presumed mechanism is paradoxical embolism via PFO, which causes the foramen ovale valve to open and trigger transient right-to-left shunt. A paradoxical embolism happens when the pressure in the right atrium raises, such as during physical activities.[6]

Recurrent stroke risk increased three-fold with the presence of PFO. Thus, PFO closure is recommended to reduce the risk of transient ischemic attack (TIA), stroke, or death from stroke, by the closure of a conduit that may cause paradoxical embolism.[7]

A current randomized clinical trials meta-analysis contrasting PFO closure measures and medical therapy in PFO patients with cryptogenic stroke/TIA has revealed new evidence. The data showed that recurrent ischemic stroke, other than TIA or all causes of death or myocardial infarction or severe side effects, is less common in patients undergoing PFO closure than those receiving medical therapy alone.[8]

PATENT FORAMEN OVALE

PFO is part of average fetal circulation. During fetal life, the blood from the inferior vena cava flows from the right to the left atrium via the PFO, bypassing the lungs. Pulmonary blood flow increases considerably during the neonatal circulatory blood transition, raising the left atrial pressure. This condition leads to compression of the primum septum against the secundum septum, functionally blocking the PFO. A PFO may form partial coalition of the primum and secundum septum.[2,5]

Primum and secundum septum starts to develop during the embryonic period, approximately 4th to 5th week of pregnancy. The primum septum starts from the postero-superior parts of the primitive atrium and arises from the midline towards endocardial cushions in the center of the heart. The secundum septum also establishes from the postero-superior parts of the atrial wall, the right side of primum septum. The concave inferior edge establishes the crista dividends (limbus of fossa ovalis). The 2nd orifice is formed because of the flap at the top of the primum septum. The orifice remained patent throughout fetal life and called the foramen ovale.[9]

During pregnancy, the foramen ovale enables blood to flow from the right atrium (RA) to the left atrium (LA). At birth, an increase in left atrial pressure reverses the interatrial gradient, pushing the primum septum to fuse with the secundum septum, thereby closing the foramen ovale. Lack of the membranous parts from the primum

and the limbus will generate PFO.[9,10]

PATENT FORAMEN OVALE EVALUATION

PFO deputize a general incidental finding on routine echocardiogram especially in the neonatal period and during childhood that requires transthoracic echocardiography (TTE). In most children, TTE with or without contrast agent is sufficient to diagnose PFO, because the resulting echocardiogram is usually very good. The subcostal cut surface provides an ideal image for detecting the presence of PFO because the diaphragm is fairly perpendicular to the transducer and has sufficient echo reflection from this location; therefore, the possibility of error and misdiagnosis of PFO is reduced. Color Doppler is required for PFO confirmation and, thus, provides evidence of transseptal flow.[9]

TTE is part of the routine examination in stroke patients. It is also a non-invasive test for PFO detection with 99% specificity. Intravenous injection of saline contrast media during the Valsalva maneuver and the visible contrast microbubbles from the right to the left atrium via the foramen ovale increase the sensitivity and diagnostics of interatrial communication.[4,5]

TTE in adult patients often produces poor-quality images, leading to a less convincing examination. TTE in children is usually better than in adults. The use of contrast media (agitated saline), acceptable Valsalva maneuvers, and harmonic imaging increase the ability to detect intracardiac and extracardiac flow.[11]

The advance of agitated saline bubbles from the right atrium to the left atrium indicates the existence of PFO. The shunt degree is assessed in three cycles, i.e., small shunt (3–10 bubbles), moderate shunt (10–20 bubbles), and large shunt (> 20 bubbles).[4] There is no uniform grading scheme that can assess the degree of diversion from right to left. However, Rana et al. A practical method is proposed. There are less than 5 bubbles in level 1, 5-25 bubbles in level 2, and more than 25 bubbles in level 3. The presence of bubbles in the entire atrial space is level 4.[12]

Transesophageal echocardiography (TEE) has historically been considered the gold standard for detecting PFO in adult patients with stroke. TEE is also needed to describe the anatomy of the atrial septum during child surgery or interventional cardiac catheterization. In some surgeries, such as tetralogy of Fallot (TOF) repair, a small PFO may be ignored or an artificial hole may be created in the atrial septum, allowing right-to-left shunting and maintaining the heart in a hypertrophic right ventricle. Small output, inadequate pulmonary artery relaxation or increased potential afterload. In this case, color Doppler may show a right-to-left split or a two-way split.[9]

PATENT FORAMEN OVALE AND IDIOPATHIC STROKE

A head computed tomography (CT) without contrast is an examination conducted to evaluate stroke patients. This examination has a high sensitivity to rule out intracranial hemorrhage. Head CT examinations are widely available and less expensive than other imaging modalities, such as magnetic resonance imaging (MRI) of the brain. However, head CT lacks sensitivity in detecting small infarcts, which are essential in detecting the mechanism of stroke.[13]

Cryptogenic stroke is a clinical syndrome comprising a focal or global neurologic deficit. It is related to the lesions on head CT or brains MRI with unknown underlying cause despite a thorough evaluation using available diagnostic procedures.[14]

Cryptogenic strokes explain up to 40% of all ischemic strokes. Since the 1980s, the relation between PFO and cryptogenic stroke has been considered. Between 40-50% of patients with cryptogenic stroke also have PFO. This finding suggests that several cryptogenic strokes, specifically in young patients, can be caused by paradoxical embolism. This condition happens when the thrombus moves from the systemic venous circulation to the systemic arterial system via the PFO and the right-to-left shunt.[3,15]

The link between PFO and stroke was initially described by Julius Friedrich Cohnheim, a German pathologist, in 1877. He performed a post-mortem examination of a 35-year-old woman with a life-threatening stroke and discovered a lengthy thrombus in her lower extremity, and a huge foramen ovale. Cohnheim theorized that a severed thrombus from the lower extremity advanced from the right atrium to the left atrium and into the frontal lobe.[2]

Several studies using TTE or TEE confirmed the relationship between PFO and cryptogenic stroke in younger patients. The stroke mechanism is hypothesized as paradoxical embolism, i.e., emboli in the systemic arterial circulation originating from a thrombus in the venous circulation. Paradoxical embolism, which is documented by detecting a thrombus attached to the PFO, is often more likely to be considered a stroke mechanism than other possibilities.[1,16] A PFO with a momentary or continuous right-to-left shunt has the ability to trigger paradoxical embolism. The PFO works as a passable channel for embolism from the veins to pass through right atrium into left atrium and finally to the arterial circulation.[2]

Several studies have demonstrated that PFO may be a significant contributor to stroke in younger patients and those with lower levels of atherosclerotic risk factors.[17] Features that increase the likelihood of a PFO and stroke association include more youthful age, a Valsalva maneuver at the onset of a stroke, long journeys by plane or car, venous thrombosis in the legs or pelvis, venous hypercoagulation state, an atrial septal aneurysm, history of migraine with aura, cortical infarct and large cerebral infarcts, and in the absence of hypertension, diabetes, and smoking habits.[18]

Laboratory studies are also valuable for determining prognosis and treatment strategies. Current research shows that the coexistence of PFO and high levels of D-dimers enhanced recurrent ischemic stroke risk in patients with PFO-related stroke.[19]

MANAGEMENT

Optimal management for patients with PFO-associated cryptogenic stroke remains questionable.[20] Medical therapy using antiplatelet with modified stroke risk factors remains the mainstay of treatment in most patients diagnosed with cryptogenic stroke, with or without PFO. Despite the growing demand for anticoagulation therapy, there is

insufficient data to determine whether oral anticoagulants (OAC) are equivalent to or better than aspirin as secondary prevention of cryptogenic stroke. Apart from traditional medical therapy using antiplatelets and OAC, PFO closure is currently a preferable option.[17]

In general, there are two ways of preventing recurrent stroke in PFO-associated cryptogenic stroke patients. One of these is transcatheter PFO closure surgery followed by administration of dual-antiplatelet agents, such as aspirin and clopidogrel, for several months. Also, medical treatment using antithrombotics, either antiplatelets or anticoagulants. PFO closure aims to avoid neurologic events and long-term use of anticoagulants. However, the advantages of PFO closure followed by antithrombotic therapy over antithrombotic therapy alone in preventing stroke recurrence are controversial.[21,22] It is unclear whether treatment with anticoagulants or antiplatelets is the optimal prevention strategy in patients with PFO-associated cryptogenic stroke who did not undergo PFO closure.[23]

A meta-analysis of 48 comparative observational studies with a total sample of 10,327 reported that patients with cryptogenic stroke or TIA obtaining medical therapy had a 6.3-fold increase in recurrent neurologic events than patients undergoing percutaneous PFO closure.[24] Percutaneous PFO closure is mainly performed for the prevention of stroke due to paradoxical embolism. A case series of patients who went through PFO closure demonstrates that percutaneous PFO closure was safe and resulted in a low incidence of recurrent stroke.[20,25]

CLOSURE I (Evaluation of the STARFlex Closure System in Patients with a Stroke and/or TIA due to Presumed Paradoxical Embolism Through a PFO) is a multicentre, open-label, and randomized clinical trial of PFO closure to prevent stroke. The study's main endpoint was a combination of stroke or TIA within two years, death from any cause within 30 days, or neurologic death between 31 days and two years. The study shows that PFO closure did not significantly benefit to prevent recurrent strokes or TIAs. The incidence of primary endpoints was 5.5% in the PFO closure group and 6.8% in the medical therapy group (Hazard Ratio [HR], 0.78; 95% Confidence interval [CI], 0.45 to 1.35; P = 0.37).[26]

Similarly, a percutaneous trial (Clinical Trial Comparing Percutaneous Closure of Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism) was published in 2013. Four hundred and fourteen patients with PFO and ischemic stroke, TIA, or peripheral thromboembolic events were randomly determined to go through PFO closure using the Amplatzer PFO Occluder or medical therapy. Patients undergoing PFO closure were given 100–325 mg/day of aspirin for a minimum of 5 months and 250–500 mg/day of ticlopidine or 75–150 mg/day of clopidogrel for 1 to 6 months. The medical therapy group was given antiplatelets or anticoagulants, as selected by the local investigators. During a mean follow-up of 4.1 years, PFO closure showed no significant reduction in the risk of recurrent embolism or death than medical therapy (3.4 vs. 5.2%, P = 0.34).[27]

In the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial, 980 patients with cryptogenic stroke were randomly divided into two groups, i.e., the medical treatment group who received antiplatelets, including warfarin, and the transcatheter PFO closure (using the Amplatzer PFO Occluder combined with dual antiplatelet therapy for one month followed by a 5-month aspirin therapy) group. The primary endpoints were nonfatal ischemic stroke, fatal ischemic stroke, or mortality shortly after randomization. At the average follow-up of 2.6 years, the study shows no significant difference in stroke recurrence between the PFO closure and medical treatment groups (9 patients vs. 16 patients) (HR: 0.49; 95% CI, 0.22 –1.11; P = 0.08).[28] In contrast, the long-term follow-up (median 5.9 years) data showed that PFO closure significantly decreased the recurrent stroke than medical therapy (3.6% vs. 5.8%; HR: 0.55; 95% CI: 0.31 to 0.999; p = 0.046).[29]

The CLOSE (Closure of PFO, Oral Anticoagulants, or Antiplatelet Therapy to Prevent Stroke Recurrence) trial is a multicentre, open-label, randomized, three-group clinical trial. At a mean follow-up of 5.3 ± 2.0 years, PFO closure significantly reduced the risk of recurrent stroke compared to antiplatelet therapy (HR 0.03; 95% CI, 0-0.26; P <0.001). Despite indicating a trend toward superiority, the anticoagulant group was not significantly beneficial compared to antiplatelet therapy (HR 0.43; 95% CI, 0.1-1.5; P = 0.17). An important indicator in this study was the elevated risk of AF with PFO closure during the periprocedural period compared to antiplatelet therapy alone (4.6% vs. 0.9%; P = 0.02).[30]

Similarly, the Gore-REDUCE clinical trial (Gore Helex Septal Occluder/Gore Septal Occluder for PFO Closure in Stroke Patients) randomized a total of 664 patients into one of the PFO closure group utilizing the Helex Septal Occluder device or the Cardioform Septal Occluder device, in addition to antiplatelet therapy, and a group of patients receiving antiplatelet therapy alone. The co-primary endpoint was free of recurrent ischemic stroke or new asymptomatic brain infarcts on imaging. At a median follow-up of 3.2 years, recurrent ischemic strokes happened less commonly in the PFO closure group than in the medical therapy group (1.4% vs. 5.4%) (HR, 0.23; 95% CI, 0.09-0.62; P = 0.04).[31]

A current meta-analysis demonstrated that PFO closure was more effective than antithrombotic therapy in restraining the risk of recurrent stroke after PFO-associated cryptogenic stroke events.[32]

CONCLUSION

The PFO is a promising pathway for embolism to pass, whether it is platelet aggregation, thrombus, air bubbles, or other particulate matter, from the systemic venous circulation to the cerebral blood vessels, causing ischemic stroke. Recent randomized clinical trials have demonstrated that in PFO-associated cryptogenic stroke patients, PFO closure with antiplatelet therapy for several months has helped decrease the risk of recurrent stroke instead of medical treatment alone.

CONFLICT OF INTEREST STATEMENT

The authors declare there is no competing interest.

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AUTHOR CONTRIBUTION

Herlina Dimiati contributed for review concept, writing the original draft and literature search. Rico Rasaki contributed for manuscript preparation and support for writing the original draft. Both of the authors had reviewed and agreed for the final version of the manuscript for publication.

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