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Contents

Review Article

Case Report

AUTHOR GUIDELINES

Indonesian Journal of Cardiology (IJC) is a peer-reviewed and open-access journal established by Indonesian Heart Association (IHA)/*Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI)* on the year 1979. This journal is published to meet the needs of physicians and other health professionals for scientific articles in the cardiovascular field. All articles (research, case report, review article, and others) should be original and has never been published in any magazine/journal. Prior to publication, every manuscript will be subjected to double-blind review by peer-reviewers. We consider articles on all aspects of the cardiovascular system including clinical, translational, epidemiological, and basic studies.

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Review Article

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Echocardiography Detection of High-Risk Patent Foramen Ovale Morphology

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Abstract
Patent Foramen Ovale occurs in 25% of the general population1. Several studies suggested that paradoxical embolism through a patent foramen ovale (PFO) correlate with cryptogenic strokes (CS). Many epidemiological and clinical observational studies showed the association between CS and the presence of PFO. There is still a controversy about whether PFO should be closed.
The information about PFO morphology might be useful for the management of PFO. This article discusses technical information about how echocardiography detects PFO and identifies high-risk morphologies for the occurrence of PFO related -stroke
.

(Indonesian J Cardiol. 2021;42:63-69)

Keywords: Echocardiography; Diagnosis; Patent Foramen Ovale.

Introduction

Patent Foramen Ovale occurs in 25% of the general population1. Several studies suggested that paradoxical embolism through a patent foramen ovale (PFO) correlate with cryptogenic strokes (CS). Many epidemiological and clinical observational studies showed the association between CS and the presence of PFO. However, studies showing inconsistent result regarding whether PFO closure reduces stroke recurrence in comparison with medical therapy. Earlier studies reported that PFO closure did not significantly reduce a composite of death and neurological events[2-4.2-4] More recent studies included some specific PFO morphologies and showed the positive result of PFO closure to reduce the outcome.[5-8] Perhaps these specific morphologies for screening the candidate could explain the different result between the earlier and later studies. Further, Nakayama et al. recognized some PFO features that might correlate with a higher incidence of neurological events and introduced a scoring system to predict.[9] A meta-analysis showed that patients with cryptogenic stroke/ TIA and PFO who have their PFO closed, ischemic stroke recurrence is less frequent compared with patients receiving medical treatment. However, after PFO closure, atrial fibrillation may occur quite frequent, though mostly transient.10 So, selecting a good candidate is important to get the most benefit of PFO closure.

The information about PFO morphology might be useful for the management of PFO. Comprehensive information regarding patient characteristics, clinical features, imaging stroke pattern, and PFO morphology is necessary to decide whether or not to close the PFO.[11]

This article discusses how echocardiography detects PFO and identifies high-risk morphologies for the occurrence of PFO related -stroke.

How to evaluate interatrial septum

Interatrial shunt occurs for approximately 6% -10% of congenital heart disease, with secundum atrial septal defect (ASD) and PFO are among the commonest lesion. However, PFO is not a true interatrial defect because there is no septal tissue deficiency present. Foramen Ovale is a flap valve-like appearance between the septum primum and septum secundum called foramen ovale located in the anterosuperior portion of the atrial septum. Failure to close the foramen ovale after birth is called patent foramen ovale. It will potentially open if the right atrial pressure exceeds the left atrial pressure causing a shunt from the right atrium (RA) to the left atrium (LA).

Transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) can recognize the presence of PFO by visualizing the interatrial septum (IAS). Some techniques used to ensure clear and good visualization of the IAS are as follows;

- We can visualize IAS from an apical 4 chamber view by TTE (fig. 1)
- Theoretically, subcostal view by TTE is a better view to show IAS, as it is perpendicular to the ultrasound beam. However, in an adult, the image quality of the subcostal view is not always adequate for comprehensive evaluation. (fig. 2) An off-axis apical 4 chamber view might shift vertical IAS to a rather diagonal position. This maneuver could improve the image quality of IAS.
- TEE is the reference modality for evaluating IAS. The image is clearer due to the proximity of the probe to the heart, and it shows IAS perpendicular to the ultrasound beam. (fig. 3) We need to scan through the IAS from 0° – 180° to get a full orientation of the IAS and the surrounding structures. This is the best way to evaluate PFO morphology.

Using 3 D TEE, we can appreciate the PFO and other structures next to it. At the superior orientation, there is superior vena cava (SVC), at the inferior is inferior vena cava (IVC), at the posterior is pulmonary veins and posterior wall of LA, and the aortic valve at anteriorly. (fig. 4)

How to evaluate PFO

Foramen Ovale is formed from the septum primum and septum secundum and appears as the thin part of IAS. The common view to appreciate PFO by TEE is from bicaval view at 90-110° (pic. 4). PFO will open if RA pressure exceeds LA pressure, resulting in a R-L shunt. With stretched PFO, the L-R shunt may occur (fig.5) Using TTE, we cannot see PFO as clear as by TEE. However, the bubble contrast test could help to confirm its presence.

We commonly use agitated saline contrast to confirm the presence of PFO with a paradoxical shunt.

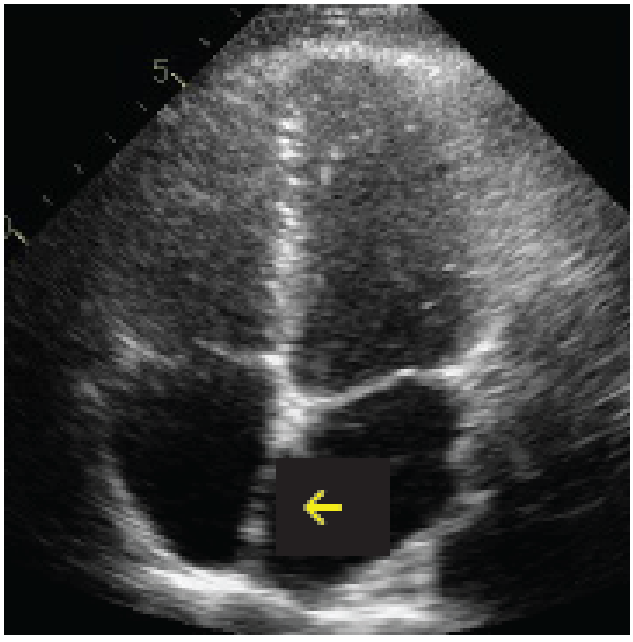

Figure 1. Transthoracic echocardiography showing 4 chamber view. Note that IAS (yellow arrow) is in a vertical position, parallel with the ultrasound beam.

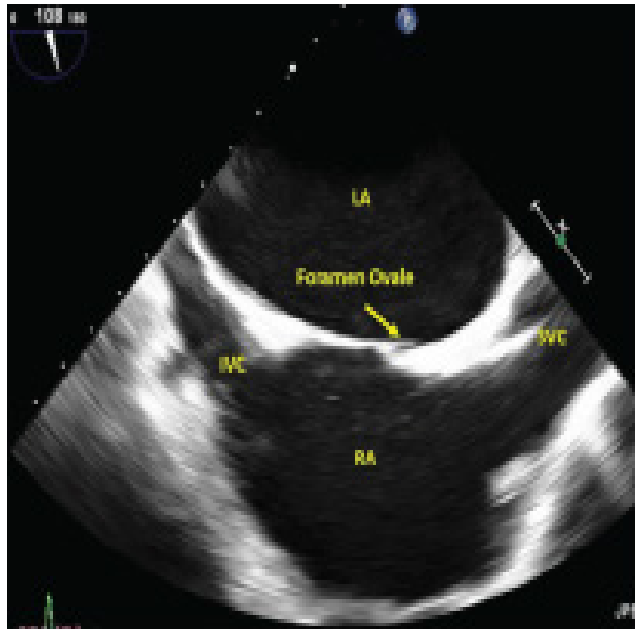

Figure 3. Bicaval view from trans-esophageal echocardiography shows a clear IAS and foramen ovale which is perpendicular to the ultrasound beam. LA; left atrium, RA; right atrium, IVC; inferior cava vein, SVC; superior cava vein.

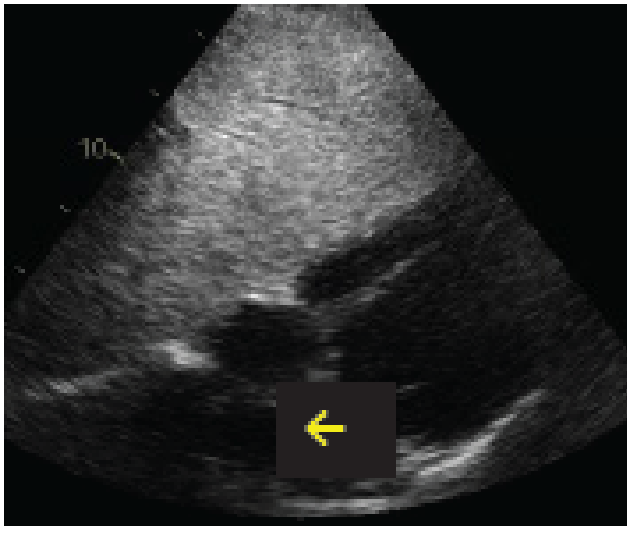

Figure 2. Transthoracic echocardiography showing the subcostal view. Note that IAS (yellow arrow) is almost horizontal, perpendicular to the ultrasound beam.

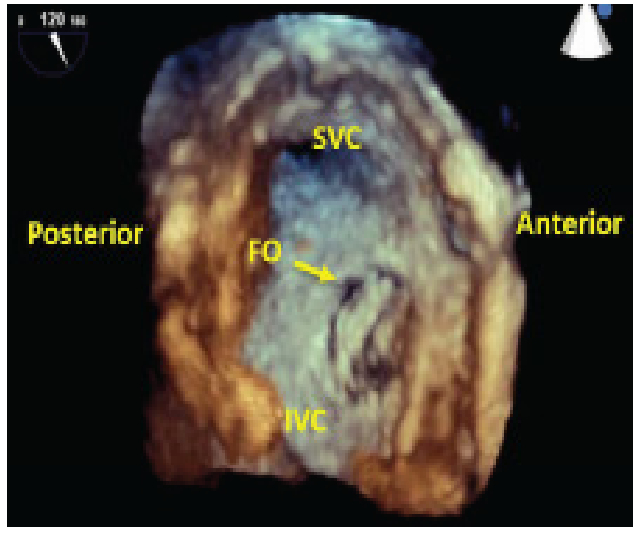

Figure 4. En face view of the IAS and foramen ovale by 3D TEE. IVC; inferior cava vein, SVC; superior cava vein, FO; foramen ovale.

The procedure can be done using either TTE or TEE. Below is how to perform an agitated saline bubble study;[12,13]

- Preparing the patient;
  - Intravenous access. Larger veins may guarantee better flow (brachial or femoral vein)
  - Use 18-20 F gauge cannula connected to 3-way stopcock
- Preparing the contrast;
  - Two 10 ml syringes
  - 50 ml saline
  - Mix 0.5 - 1 ml blood + 9 ml saline + just enough air (0.2 ml) in one syringe
  - Connect that syringe to the other one with 3-way stopcock
  - Prepare the solution by rapidly agitating between the two syringes several times until the fluid mixed homogeneously with very fine bubbles.
- Performing the test;
  - Find the best echo view for PFO visualization. TEE 90-110° or TTE the apical 4 chamber view with vertical IAS (avoid diagonal IAS, as it may create reverberation in the LA while contrast enter the RA)
  - The solution is injected rapidly. Wait until it creates full opacification of RA. Then, evaluate whether some bubbles appear in the left heart.
  - Ten beats acquire digital loop is to capture the process, from just before bubbles enter the RA.
  - If Valsalva manoeuvre is to perform, the patient has to hold in strain phase until bubbles enter the RA, and release Valsava as bubbles fill the RA (and start counting the beats).

Positive bubble contrast test is considered when some bubbles occur in the left heart within three beats after opacification of the RA. The false-negative result may occur if the Valsalva manoeuvre is not adequate to drain the bubble from the RA to the LA through PFO. Because the preferential flow through the PFO is coming from the IVC, performing bubble contrast from the femoral vein access might increase the sensitivity of the test and avoid the false-negative result. The false-positive result may occur if there is of pulmonary artery-venous malformation. If the bubbles appear in the left heart beyond 3 beats after the RA opacification, it is more likely that the bubbles cross through the pulmonary shunt, instead of the PFO.

High-risk morphology of PFO

Some PFO morphologies might correlate with a higher incidence of neurological events, and TEE can recognize the features quite well. Nakayama et al. introduced a scoring system of PFO morphology to predict the risk of CS (table 1). Using five variables with one point for each positive variable, they concluded that > 2 points were associated with the higher possibility of CS.[9] A systematic review and meta-analysis evaluated the morphology of the PFO as a risk factor for cerebrovascular accident.[14]

Table 1. High-risk Patent Foramen Ovale (PFO) Score.

Variables	Point
Long-tunnel PFO > 10 mm	1
Hypermobile interatrial septum	1
Eustachian valve or Chiari's network	1
Large Right -Left shunt during Valsalva maneuver	1
Low-angle PFO < 10°	1
Maximal total point	5

A total point of > 2 is defined as a higher association with the cryptogenic stroke

Next is some echocardiography features of the high-risk PFO morphology and best evaluated by TEE;

1. ***Long-tunnel PFO > 10 mm***
   Using TEE at 90-110°, it is the maximum overlap between the septum primum and septum secundum (fig. 6)
2. ***Hypermobility of interatrial septum***
   Atrial septal aneurysm (ASA) is defined when septal excursion from the midline into either the RA/ LA is > 10 mm, or the total excursion between the RA to LA> 15 mm. While hypermobile IAS was defined as the excessive motion and floppy IAS with an excursion of each heartbeat reaches > 5 mm (fig.7).
3. ***Presence of Eustachian valve or Chiari's network***
   This feature is one of the scoring variables and considers positive if seen as > 10 mm protrusion within the RA (fig 8 and fig 10).
4. ***Large R-L shunt during Valsalva maneuver***
   Using an agitated saline contrast test with or without

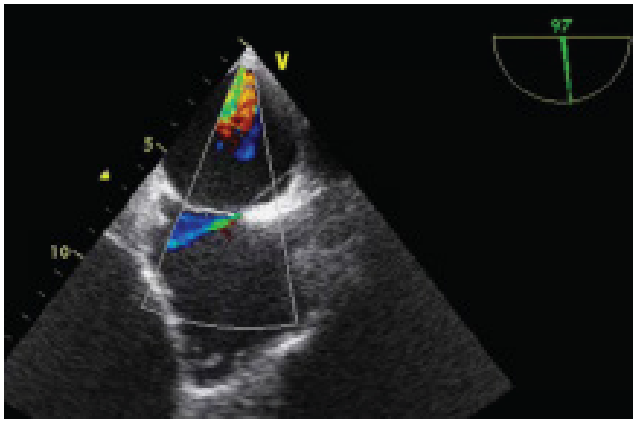

Figure 5. TEE showed stretched PFO with L-R shunt.

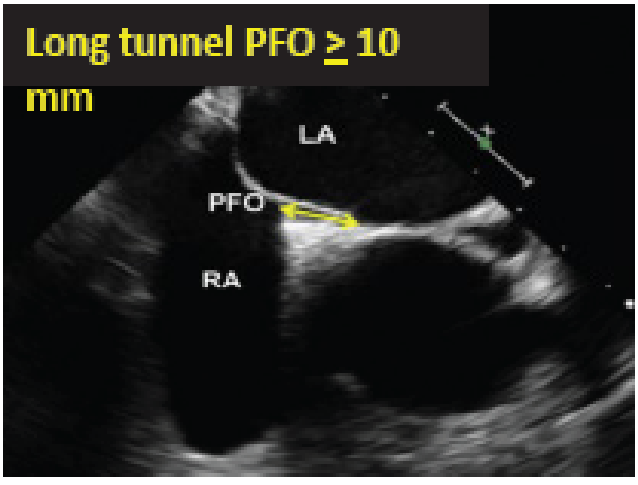

Figure 6. TEE showed long tunnel PFO, which is one of the high-risk features associated with cryptogenic stroke. LA; left atrium, RA; right atrium, PFO; patent foramen ovale. The picture was taken from reference [10].

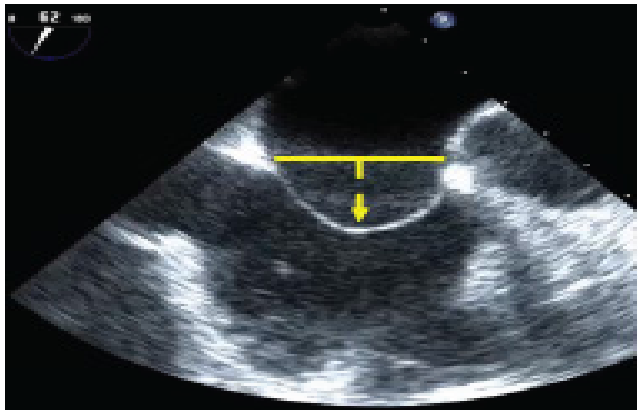

Figure 7. TEE showed atrial septal aneurysm (ASA) with > 10 mm septal excursion from the midline into the right atrium.

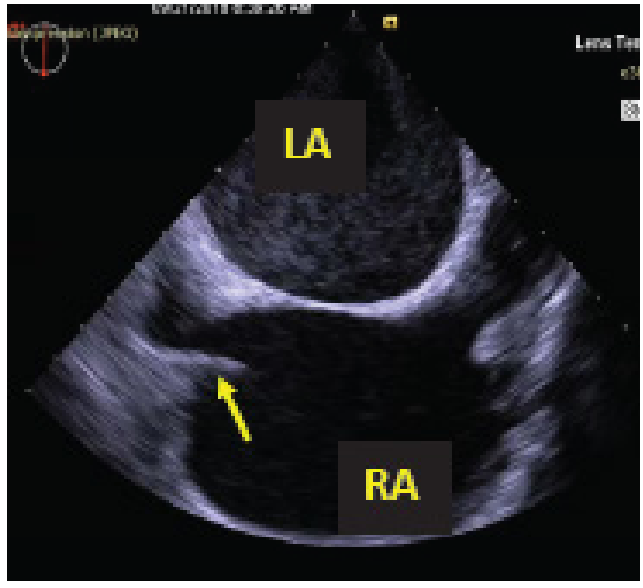

Figure 8. From TEE, yellow arrow showed Eustachian Valve.

Valsalva maneuver, we visualize the LA's bubble appearance within 3 beats after full opacification of the RA. The large RL shunt was defined as > 20 microbubbles. The result can be detected by TTE (fig 9a) or TEE (fig 9b). For the detailed procedure, refer to the above information about how to perform a bubble contrast test.

5. ***Low-angle PFO < 10°***
   Using TEE from bicaval view (at around 90-110 °), we can measure the angle between IVC and PFO flap on and < 10° was defined as low-angle PFO (fig 10).
6. ***Large-size PFO, > 2 mm***
   This feature was not included in the score, but still an important feature that might correlate with the risk of CS. Using TEE, large-size PFO is defined when the maximum separation between the septum primum and septum secundum reaches> 2 mm, at the end-systolic frame (fig.11).

Summary

As discussed above, PFO is a relatively common condition in the general population. There are still controversies regarding its correlation with CS and whether it should be closed in all PFO cases. Some studies recognized some PFO features that might

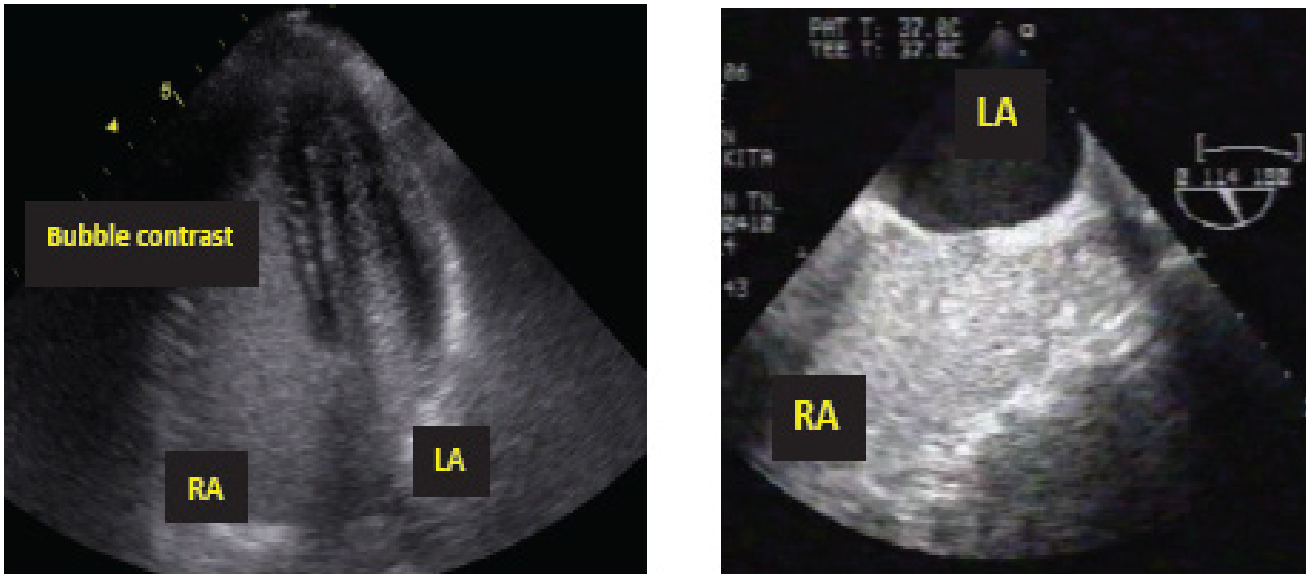

Figure 9. This picture shows a bubble contrast test performed in two different patients. Noted the full opacification of the RA. TTE visualizes a positive bubble contrast test with a large right-left shunt in the 1st patient (fig 9a.), and the negative result showed from TEE in the 2nd patient (fig 9b) .

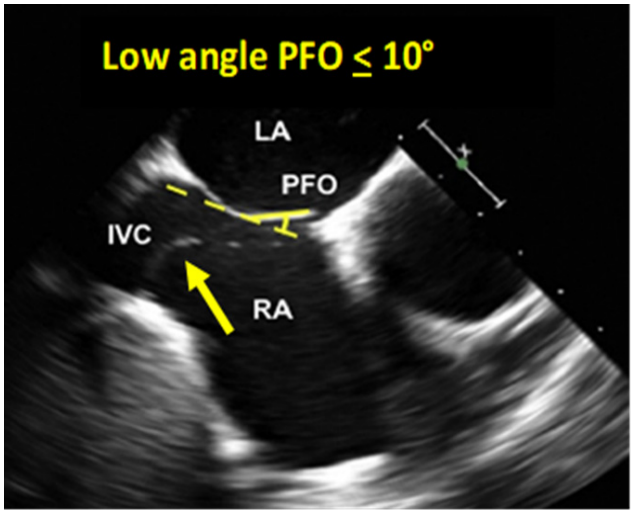

Figure 10. TEE showed low angle PFO – IVS. Noted yellow arrow showed Chiari's network. LA; left atrium, RA; right atrium, PFO; patent foramen ovale, IVC; inferior cava vein. The picture is taken from reference. [10]

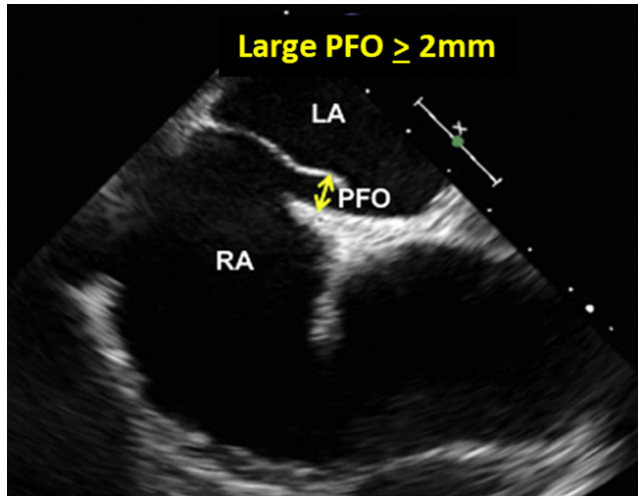

Figure 11. TEE showed a large separation of both primum and secundum septum, creating a wide gap. LA; left atrium, RA; right atrium, PFO; patent foramen ovale. The picture is taken from reference. [10]

correlate with CS. Using echocardiography, we can identify the presence of PFO and appreciate the high-risk morphology of PFO.

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Review Article

Patent Foramen Ovale (PFO) Implying Paradoxical Embolism as a New Insight in Cryptogenic Stroke

Indah Aprianti Putri

Abstract

Background: Cerebrovascular thromboembolism is responsible annually for 510.000 ischaemic stroke in the united states alone. PFO mechanism as a paradoxical embolism transit from right to left-sided chambers to intracranial vessels has a tremendous impact in neurological deficits. The aggressive treatment started since 2016 when the US Food and Drug Administration (FDA) approved the Amplatzer PFO occluder for recurrent stroke prevention of cryptogenic stroke with PFO. The trials show positive results since 2017 and the collaboration and partnership between neurologist and cardiologist are more needed to build a holistic and comprehensive treatment for cryptogenic stroke patient with PFO.

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Keywords: cryptogenic stroke, PFO, paradoxical embolism, PFO occluder, comprehensive treatment.

Introduction

Ischaemic stroke is one of the leading causes of mortality and morbidity in the world. Globally, there are more than 1.2 million stroke survivors. It is a devastating disease with clinical manifestations as focal or global neurological deficits. Patients with ischaemic stroke have negative effects on their quality of life with loss of their cognitive capacity and physical capabilities. Stroke survivors need the prevention from recurrence of ischaemic stroke events.[1-3]

Mostly, ischaemic stroke aetiologies are classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. By this classification, usual mechanisms of ischaemic stroke include stroke secondary to large vessel disease (clot at carotid or part of large vessel of intracranial vessels), cardioembolic events, small vessel occlusion (lacunar infarct, leukoariosis and microbleeds), other identified cause (criptogenic stroke or embolic stroke of undetermined source or ESUS) or have no determined cause.[4]

AAnother group of sub-types of ischaemic stroke is ASCOD. This classification system offers objective criteria for Atherosclerosis/atherothrombosis, Small vessel disease, Cardioembolic stroke, Other causes such as criptogenic stroke, and Dissection.[4]

About 20-30% of cryptogenic strokes are associated with PFO . Since 2017, studies have shown significant treatment of patent foramen ovale (PFO) closure in criptogenic stroke which has implying paradoxical embolism as the mechanism of this stroke in this group of sub-types. This means that a management of team work between neurologist and cardiologist will improve the beneficial treatment for preventing recurrent of ischaemic stroke.[4]

PFO in Cryptogenic Stroke (Embolic Stroke of Undetermined Source or ESUS)[5-6]

Most criptogenic strokes are embolic, the sources are coming from:

- **Cardiogenic embolism** such as unrecognized paroxysmal atrial fibrillation or atrial high-rate episodes/atrial systole.
- **Paradoxical embolism** via patent foramen ovale (23% of the population) or other right (R) to left (L) intra-cardiac shunt.
- **Arteriogenic embolism** for example aortic arch atheroma with ulceration or thrombi, non-stenotic ulcerated cervical carotid atheroma, non stenotic intracranial large artery atheroma.

Paradoxical embolism in Criptogenic stroke via PFO based on ESUS criteria:

1. Acute brain infarct visualized on neuroimaging that is non lacunar.
2. Absence of occlusive proximal atherosclerosis.
3. No major-risk cardioembolic source with normal heart rhytm.
4. No other likely cause of stroke (such as dissection, arteritis).

Neurological Manifestation to Diagnose PFO in Cryptogenic Stroke[7]

The manifestation of neurological symptoms in criptogenic stroke are based on BAMFORD study[6-7]. The Bamford classification consists of the following types of ischaemic stroke:

- Total Anterior Circulation Infarction (TACI) cortical stroke in middle or anterior cerebral artery territory. Patients are diagnosed by all three of the following:
  1. Unilateral weakness (and/or sensory deficit) of face, arm, or leg.
  2. Homonymous hemianopia.
  3. Higher cerebral dysfunction (dysphasia, visuospatial disorder).

- Partial Anterior Circulation Infarction (PACI) cortical stroke in middle or anterior cerebral artery areas. Patients are diagnosed by two of the following:
  1. Unilateral weakness (and/or sensory deficit) of face, arm, or leg.
  2. Homonymous hemianopia.
  3. Higher cerebral dysfunction (dysphasia, visuospatial disorder).

- Posterior circulation infarction (POCI), the diagnosis is made if the patient has one of the following:
  1. Cerebellar or brainstem syndrome.
  2. Loss of consciousness.
  3. Isolated homonymous hemianopia.

- Lacunar infarction (LACI) - subcortical stroke due to small vessel disease, there is no evidence of higher cerebral dysfunction. Diagnosed by one of the following symptoms:
  1. Pure Motor Stroke.
  2. Sensorimotor Stroke.
  3. Pure sensory stroke.
  4. Ataxic hemiparesis.
  5. Dysarthria-clumsy hand.

How to Diagnose PFO in Cryptogenic Stroke

How to diagnose PFO in criptogenic stroke need some evidence that in the further diagnostic examination shows that no evidence by the cause related to large vessel, small vessel, cardioembolic stroke such as atrial fibrillation. It is also not related with other causes such as dissection, or others paradoxycal embolism and hypoperfusion.

PFO is a main cause of left circulation of heart thromboembolism in criptogenic stroke with other clues for example young age, within a limited vascular risk factors of the patient history of medical illness. High risk of PFO will more suspicious if some evidences such as :

- D dimer > 1000
- First event of ischaemic stroke with non lacunar infarction from brain CT or MRI
- Absence of cervical carotid atherosclerotic artery stenosis > 50% or occlusion
- No atrial fibrillation after >24 hours cardiac rhytm monitoring
- No intra-cardiac thrombus on echocardiography
- No history of antiplatelet or anticoagulant
- History of hypercoagulable state
- Evidence of PFO from TEE bubble
- Large inter-atrial shunt or an strial septum aneurysm (ASA) positive from echo
- TCD bubble test positive with RoPe score need to do to evaluate patient risk of recurrent ischaemic stroke.[8-10]

TCD Bubble Test

Transcranial Doppler (TCD) is the only real-time technique (Figure 1 and 2) for finding emboli from extra-cranial carotid plaque or cardiac embolism by continuous monitoring and detection of micro-embolic signals or high intensity transient signals (MES or HITS) in cerebral circulation.[11]

MES can be identified as a short lasting (<0.01-0.03s), unidirectional signal with an intensity increase (>3 DB) within the Doppler frequency spectrum. MES appears randomly within the cardiac cycle and produces a" whistling", "chirping" or "clicking" sound when passing through the sample volume.[12]

Figure 1. Technique position of a patient undergoing TCD (Courtesy of the Author).

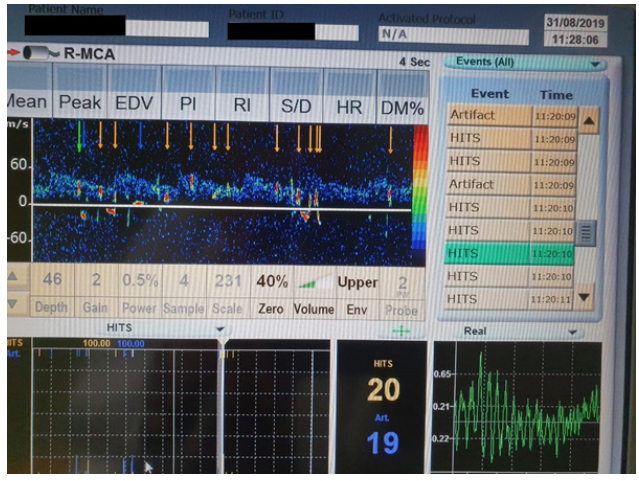

Figure 2. MES or HITS appearances (Courtesy of the author).

The grading of Spencer is a guidance for neurologist to make a diagnostic of suspected PFO in cryptogenic[13] :

- Grade 0, no microemboli
- Grade 1, 1-10 microemboli
- Grade 2, 11-30 microemboli
- Grade 3, 31-100 microemboli
- Grade 4, 101-300 microemboli
- Grade 5, >300 microemboli

Treatment PFO in Cryptogenic Stroke

The treatment of cryptogenic stroke with anticoagulant and antiplatelet based on COMPASS study. Red clot and white clot mechanism of cryptogenic stroke need anticoagulant and antiplatelet to lysis the clot of cryptogenic stroke.[14]

Treatment with rivaroxaban 2.5 mg and aspirin 100 mg are indicated for reccurent ischaemic stroke in ESUS patients with moderate-severe left atrial enlargement (LA diameter > 4.6 cm). Another study is ARCADIA trial, the hypothesis state that apixaban is superior to aspirin for prevention of recurrent stroke in patients with ESUS and atrial cardiopathy.[15]

Percutaneous PFO closure has been studied for more than two decades, marked by a series of negative, underpowered and inconclusive trials. In 2016, the US Food and Drug Administration approved the Amplatzer PFO occluder for recurrent stroke prevention. Historically, support for PFO closure has been stronger among cardiologist-especially interventional cardiologist-than among neurologist. What we knew related into treatment of PFO, 3 trials namely Closure trial, PC trial (Percutaneus Closure of PFO in criptogenic embolism) and RESPECT trial (Randomized Evaluation of Reccurent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) published before 2017 did not show any benefit of PFO closure over medical treatment in reducing recurrence stroke in patients with cryptogenic stroke associated with PFO.[16]

CLOSE trials as randomized, open label, superiority trial conducted in Europe. The participants were 16-60 years old and enrolled from December 2007 through December 2014 and followed up until December 2016. The participants had recent (≤ 6 months) cryptogenic stroke attributed to PFO with an atrial septum aneurysm or large inter-atrial shunt.

Eligible patients were randomly assigned, in a 1:1: ratio, to undergo PFO closure followed by long term antiplatelet therapy (PFO closure group), or to receive antiplatelet therapy alone (antiplatelet group), or oral anticoagulant (anticoagulant group). The primary efficacy outcome was the occurance of any stroke. The secondary efficacy outcomes were the composite of ischaemic stroke, transient ischemic attack (TIA) or systemic embolism; disabling stroke (defined as mRS ≥ 3), death from vascular-related causes; success of device implantation, and success of PFO closure. The safety outcomes were procedural or haemorrhagic complications. A clinical events committee blindly adjudicated outcome events. Patients were followed up at 2 months, 6 months, and thereafter 6 months by direct visit while telephone visits were performed for those beyond 5 years of follow up. Six hundred and sixty-three patients wre enrolled into the study and followed for mean (± SD) 5.3±2.0 years. In the comparison of PFO closure group versus antiplatelet only group, there was no stroke reported among the 238 patients in the PFO closure group, whereas 14 of 235 patients in the platelet only group had stroke (P<0.001).[16]

The number needed to treat (NNT) to prevent one stroke is 17 at 5.3 years or 90 if considered annually. Among those who underwent PFO closure, 14 patients (5.9%) had procedural complication. Although, the rate of atrial fibrillation was higher in the PFO closure group than in the antiplatelet-only group. Serious adverse events did not differ significantly between these 2 treatments group. In the analysis of antiplatelet group versus anticoagulant group, stroke occurred in 3 of 187 patients (1.5%) with anticoagulant versus 7 of 174 patients (3.8%) assigned to antiplatelet therapy alone (P=0.18). The bleeding complications and serious events did not differ significantly, probably as a result of the small number of participants in this comparison.

For young and middle aged persons with cryptogenic stroke associated with high risk PFO there is now some randomized trial evidence to support PFO closure namely Gore REDUCE trial. The investigator conducted a multinational randomized trial including patients with cryptogenic stroke and PFO with right to left shunt. Approximately 81% had a moderate or large shunt. Patients were enrolled from 63 centers

including 664 patients with cryptogenic stroke and PFO. These patients were randomly assigned in a 2:1 ratio to undergo PFO closure with antiplatelet therapy or antiplatelet therapy alone respectively. Of the 664 patients, 441 patients were randomized to PFO closure group and 223 patients were assigned to the antiplatelet alone group. The primary outcomes were the percentage of patients with clinically evident stroke and combined incidence of clinical ischaemic stroke and silent brain infarction on imaging through at least 24 months follow up post-randomization. Median follow up was 3.2 years.

The investigators found that patients who underwent PFO closure with antiplatelet therapy had a significantly lower incidence of clinical ischaemic stroke (1.4%) as well as new brain infarction (5.7%) as against antiplatelet therapy alone group who had 5.4% and 11.3% incidence of clinical ischaemic stroke and silent brain infarction respectively.

6.6% of patients in the PFO closure group had atrial fibrillation or flutter. Of which at least 415 persisted more than two weeks. The NNT to prevent recurrent clinical ischaemic stroke over 3.2 years was 25. The NNT to prevent recurrent clinical ischaemic stroke per patient year based on this trial is 77.

This randomized trial gives evidence regarding the efficacy of PFO closure in reccurent stroke reduction in patients under 60 years of age with moderate to large interatrial shunts and cryptogenic stroke.[16-17]

Based on those trials, it needs more randomized trial data are required to consistently establish the efficacy and safety of PFO closure in preventing recurrent stroke and to find high risk sub-group of patients who could benefit significantly from procedure.

Conclusion

Long term safety of PFO closure procedure needs to be established given the fact there is increased incidence of atrial fibrillation or flutter in the PFO closure group. Neurologist and stroke clinicians evaluating very high-risk patients for PFO closure do now have some evidence that supports closure and refer the procedure to interventional cardiologist.

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Review Article

Patent Foramen Ovale Closure Procedure

Doni Firman, Arwin Saleh Mangkuanom

Abstract
Patent foramen ovale (PFO) is strongly associated with cryptogenic stroke. Various clinical trials has shown the association between cryptogenic stroke and incidence of undelrying PFO, these trials also shown the decrease of cryptogenic stroke incidence with the treatment of PFO Lesion. In the absence of absolute contraindications, patients with PFO are advised to undergo closure. Preprocedural examinations such as trans esophageal echocardiography and pretreatment with anticoagulants are required to prevent peri and postprocedural adverse events. Currently, PFO Closure can be done through a percutaneous access with minimal risk. Treatment of PFO can help decrease future incidences of strokes

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Keywords: structural; interventional; PFO; percutaneous; stroke

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Introduction

Patent Foramen Ovale (PFO) is being thought to be one of the factors causing cryptogenic stroke and about 40% patient cryptogenic stroke has PFO.[1] It takes centuries & there are numerous lessons to be learned from the PFO history until an effective treatment. In 1490, DaVinci first describe communication between the atria in pigs and ox. Virchow in 1570, first mentioned about physiologic importance of the structure in the fetal circulation & the phenomenon of embolization in the vascular system. Julius Cohnheim one of Virchow's students, in 1877 described a paradoxical embolism through the PFO. Starting in the 1900s the closure of PFO was considered as one of the effective therapies. Blakemore in 1939 & Murray in 1948 did the first surgical PFO closures. Finally, in 1992, the first percutaneous PFO closures were conducted by Lock-in 36 patients with known right-to-left atrial shunting and presumed paradoxical emboli.[2,3]

Previous studies on PFO Closure

Since then a lot of devices have been made & design specially for PFO closure from many factories, but unfortunately, not all of them could perform equally well. As an example the STARFlex Septal Closure System (NMT Medical Inc., Boston) of the CLOSURE I trial, 2012, demonstrated lower implantation success and closure rates (89% and 86%, respectively) than other PFO occlusion devices at that time, on other hand, it also showed no significant advantage of PFO closure makes dampened the enthusiasm tremendously for doing this procedure. The Incidence of post-implantation atrial fibrillation and atrial thrombus formation at 6-month rates was relatively high (5.7% and 1.1%, respectively) that cause stroke in half of the patients who have thrombus.

Long-term follow-up trials examining the effectiveness of devices for the prevention of an event, the risk of which is low at baseline and cumulative over time was well demonstrated by the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care) trial which randomized 980 stroke patients to PFO closure versus medical management.[4] In the short-term analysis (2.6-year median follow-up), there was a strong trend toward a benefit for PFO closure but did not reach statistical significance (P = 0.08). However, after a long-term follow-up of 5.9 years, RESPECT showed a more pronounced, now statistically significant stroke risk reduction with PFO closure compared to medical therapy.

Appropriate patient selection is another important lesson, these kinds of criteria have been described well from several trials, and all of them showing a benefit of PFO closure compared to medical therapy alone. In the RESPECT trial, only patients with PFO who had objective evidence of a stroke by neuroimaging were enrolled.[5] CLOSE (PFO Closure or Anticoagulation vs. Antiplatelets after Stroke) trial, including only patients with an atrial septal aneurysm or large shunt.[6] DEFENSE-PFO (Cryptogenic Stroke and High-Risk PFO) trials conducted in Korea, having only those with a hypermobile interatrial septum, atrial septal aneurysm, or a separation of the septum primum from secundum of 12 mm as an inclusion criterion.[7] REDUCE (PFO Closure or Antiplatelet Therapy for Cryptogenic Stroke) trial, exclude patients with evidence for small vessel ischemic disease, i.e., prior lacunar infarct(s), uncontrolled diabetes mellitus or hypertension, autoimmune disease, and alcohol abuse.[8]

Indications and Contraindications for PFO Closure

In real-world clinical practice, it is not that simple to prove cryptogenic stroke related to PFO and then to make decisions for PFO closure. The RoPE score helps us to calculate the possibility of cryptogenic stroke caused by PFO, it is also can be used to predict the risk of recurrent stroke and mortality risk after the PFO closure procedure. RoPE score of ≤ 6 indicates a high risk of recurrent paradoxical embolism and mortality after PFO closure.[9]

Meta-analysis of Randomized Controlled Trials (RCT) has shown the benefit of PFO closure to reduce the risk of recurrent stroke in high-risk patient criteria.[10] According to a meta-analysis of absolute mean reduction in the risk of recurrent stroke at PFO closure is only 1.0 per 100 patients per year, however, long-term prevention of secondary stroke prevention in young patients should be considered.[11] In RESPECT, CLOSE dan REDUCE trial, participants who enrolled were categorized as a young adult below 60 years old with an average of 51,2

years old in DEFENSE trial.[5,6,8,7] Other meta-analyses showed that PFO closure increases the incidence of new-onset atrial fibrillation and atrial flutter compared to medical treatment only.[12]

When patients came with a cryptogenic stroke, age under 60 years old & have an indication for PFO closure, it is recommended to have a team who systematically review & make a decision for the PFO closure procedure as seen in picture 1, which consist of multidisciplinary specialist doctors.

PFO closure is recommended in patients with cryptogenic stroke who have been well investigated systematically and have high-risk morphology of PFO. PFO closure is not recommended in pregnant cryptogenic stroke patient and one who cannot receive antiplatelet treatment after the procedure.

PFO Closure Procedure

Percutaneous PFO Closure can be performed in a standard catheterization laboratory under fluoroscopic and Transesophageal Echocardiography (TEE) guidance. General anesthesia is almost required to facilitate TEE. Adequate anticoagulation using unfractionated heparin 80-100 IU/kg body weight, administered intravenously. The femoral vein is used as a puncture site, crossing the PFO channel using Multipurpose (MP) Catheter 6F with guidewire & directly to the left upper pulmonary

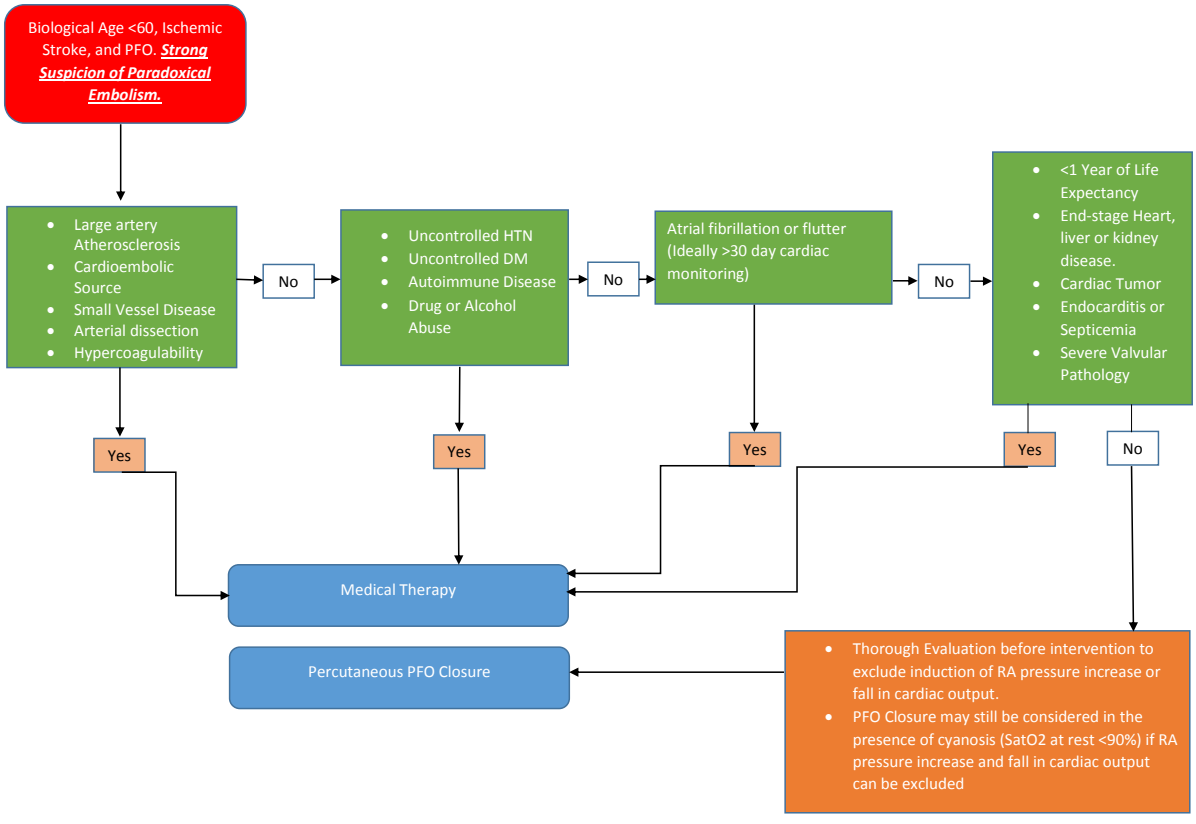

Figure 1. Evidence-Based Algorithm for PFO Closure in Ischemic Stroke Patients for Highest Clinical Yield, Based on Randomized Trials and Guidelines. (Adapted from Mojadidi et al Cryptogenic Stroke and Patent Foramen Ovale. J Am Coll Cardiol 2018;71(9):1035-1043 and Baumgartner et al, 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Heart J. 2021;42(6):563-645.). [13,14]

vein. PFO lesion sizing can be done using a balloon with angiographic analysis or by TEE image which can obtain information more accurately. A left anterior oblique fluoroscopy projection will show a good septum profile.

After sizing the PFO, an appropriate device including its delivery sheath can be selected. MP catheter then can be changed to the selected delivery sheath. To minimize the risk of air emboli, during this step de-bubble and flushing the catheter is crucial. The left atrial disc is deployed gradually start from the upper left pulmonary artery while keeps pulling back to PFO and then deploy the right disc. Confirmation of adequate position using echocardiography and fluoroscopy should be performed once the device is placed before its final release.

Antibiotic regimen after the procedure is based on local hospital policy.[12] Antithrombotic therapy with dual antiplatelet (DAPT) are given for 6 months after the procedure then after that single antiplatelet therapy could continue for 5 years depending on clinical features of the patient including recurrent thromboembolic & bleeding risk.

Transthoracic Echocardiography (TTE) evaluation is done before patient discharge and the sixth week to exclude pericardial effusion and device embolization. Routine TEE performed If only there is a significant residual PFO leakage or recurrent clinical stroke & c-TCD is performed on the sixth month after. c-TCD evaluation is carried out every year for 5 years. Complete closure is varying from each patient's endothelialization of the device and can take up to sixth months.

The complication rate is about 1 in 14 patients undergoing transcutaneous PFO closure, especially in older ages.[15] Major adverse events could happen related to the procedure, including death, stroke, air emboli, device embolization, vascular complication, bleeding complication, Atrial Fibrillation (transient or sustained), myocardial infarction, pericardial effusion with or without tamponade. Some postprocedural major adverse events are stroke, deep vein thrombosis or pulmonary embolism if occurring within 6 months after the procedure, atrial fibrillation, atrial flutter, ventricular tachyarrhythmias, or complete heart block requiring pharmacologic therapy or cardioversion, Thrombus on the device detected, pericardial effusion, device erosion, device explantation.[16]

Requirements for PFO Closure

There are several requirements for operators and institutions who are allowed to performed transcutaneous PFO Closure. These requirements are taken from the SCAI expert consensus statement on the operator and institutional requirements for PFO closure for secondary prevention of paradoxical embolic stroke 2019 and have been modified.[16]

Operator Requirements

1. Should have comprehensive knowledge of atrial/ PFO anatomy dan imaging
2. Have experience at least 50 cases of structural intervention with either minimum of 25 cases involving septal intervention or 12 cases of PFO intervention procedures under proctor or mentor.
3. Experience with catheter-based management of potential complications, including pericardiocentesis, recognition of device malposition, and embolized device retrieval

Institution Requirements

1. Have experience at least 75 cases of structural intervention in the last 5 years.
2. Done at least 25 cases of structural intervention per year with a minimum of 10 cases involving septal intervention.
3. Have a multidisciplinary team that includes necessary staff and expertise for perioperative evaluation, performing the PFO closure procedure, and acute and long-term postprocedural follow-up
4. Have catheterization laboratories that have been standardized by the Indonesian government authority.
5. Have good access to the cardiothoracic surgery theater to overcome the adverse event that might be happening.
6. Strongly recommended to have a PFO Closure registry.

Before the PFO closure procedure, it must be ensured that the patient and his family received information about periprocedural preparation, the intraprocedural process including the risk of adverse events, and postprocedural treatment. Education for

the patient is also mandatory to increase the patient's awareness and adherence to long-term medication and treatment.

Conclusion

Closure of Patent Foramen Ovale lesion should be done in all clinically eligible patients to improve quality of life and to prevent recurrence of paradoxical embolism. Assessment of patient eligibility can also be done more easily using available scoring sytems. With the advances in medicine, closure of patent foramen ovale can be done safely through percutaneous access. Percutaneous access can help PFO Closure to be more widely available across centers.

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Review Article

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Cryptogenic Stroke: Cardiac Rhythm Monitoring as An Indispensable Screening Modality

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Abstract
The prevalence of stroke in Indonesia increased over time. Cryptogenic stroke (CS) ranges from 15 to 40% from all ischemic strokes. Atrial fibrillation is predicted as one of the etiologies behind CS. As episodes of AF, in particular paroxysmal AF (PAF), were difficult to diagnose by usual diagnostic modalities, strategies based on longer rhythm monitoring should be considered to evaluate patients with CS. Innovations in digital health technologies will further help the diagnosis and management of patients with PAF.

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Keywords: Cryptogenic stroke; Atrial Fibrillation; Holter monitoring; Electrocardiogram

Introduction

The prevalence of stroke in Indonesia increased over time. Cryptogenic stroke (CS) ranges from 15 to 40% from all ischemic strokes. Atrial fibrillation is predicted as one of the etiologies behind CS. As episodes of AF, in particular paroxysmal AF (PAF), were difficult to diagnose by usual diagnostic modalities, strategies based on longer rhythm monitoring should be considered to evaluate patients with CS. Innovations in digital health technologies will further help the diagnosis and management of patients with PAF.

According to the World Health Organization (WHO), stroke is the second most common cause of death and the third most common cause of disability worldwide1. In Indonesia, stroke is the leading cause of death and accounts for 15.4% of death in almost all hospitals.[2] Cryptogenic stroke (CS) is defined as ischemic stroke with undefined etiologies after being evaluated comprehensively.[3] Clinically, the diagnosis of CS can also be considered when assessments are inadequate or etiologies are multiple. CS ranges from 15 to 40% from all ischemic strokes.[4]

Many have hypothesized explanations behind the occurrence of stroke but to no avail. CS poses a particular clinical dilemma as, without clear etiology, an educated guess is the most appropriate treatment modalities subsequently.[5] Moreover, understanding the etiology of ischemic stroke is important to prevent recurrence as stroke has a high cost of illness, with an annual approximation of 27 billion euros (IDR >465 trillion).[1]

Etiology behind Cryptogenic Stroke

Finding the etiology of ischemic stroke is important to prevent a recurrence. Patent foramen ovale, PAF, aortic arch atherosclerosis, substenotic atherosclerosis, atrial cardiopathy, and LAA dysfunction are several possible pathophysiologies implicated in cryptogenic stroke.[6] A systematic review by McMahon et al.[7] recommended several diagnostic modalities to investigate the cause of cryptogenic stroke, including brain imaging with non-contrast CT scan and MRI, vascular imaging with Coronary Computed Tomography Angiography (CCTA), magnetic resonance angiography (MRA), or Doppler ultrasound, laboratory tests, cardiac imaging, and cardiac monitoring.

The recommended laboratory tests are complete blood count, electrolytes, coagulation, renal function, random glucose, troponin, and others. Echocardiography is done to monitor cardiac structure when a cardioembolic mechanism is suspected. Last but not least, 12-lead ECG is mandatory for all patients to assess the cardiac rhythm. ECG monitoring has to be prolonged in acute embolic ischemic stroke or TIA with an unknown source to prevent the overlook of atrial fibrillation.

Atrial Fibrillation and Cryptogenic Stroke

Despite the recommendation regarding post-stroke rhythm monitoring, the evidence-practice gap still leads to a high number of patients diagnosed with cryptogenic stroke. This fact indicates the failure to diagnose the possible pathophysiology implicated in CS.[8] One of the most underdiagnosed conditions is PAF because of its intermittency and asymptomatic nature. Many times, the first clinical manifestation of PAF is stroke.[9] Data from *the Indonesian Registry on Atrial Fibrillation* (OneAF) showed that more than 30% of outpatient AF patients were asymptomatic.[10,11] Therefore, better cardiac rhythm monitoring for post-stroke AF detection is needed.

Cardiac rhythm monitoring for AF detection

Cardiac rhythm monitoring is comprised of an insertable cardiac monitor (ICM) and ambulatory cardiac monitor. Implantable loop recorder (ILR) is one type of ICM, while 24-hour ECG monitoring and cardiac event recorder using telemetry are examples of conventional ECG monitoring.

Two large randomized controlled trials, the Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL-AF) and the 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) trial have shown that longer ECG monitoring using both types of devices above in patients with cryptogenic stroke led to higher detection rates of AF, which will impact the subsequent treatment option.[9,12,13]

The CRYSTAL-AF trial comprised of 441 patients with cryptogenic stroke were either monitored using ICM ≥6 months or conventional ECG monitoring

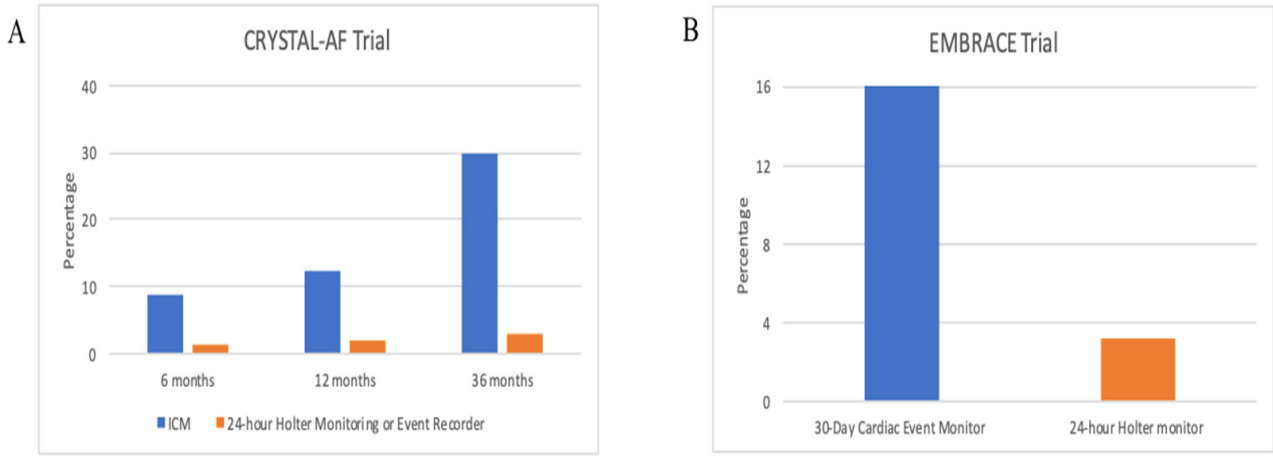

Figure 1. Higher Detection Rate with Prolonged Monitoring from CRYSTAL-AF (Cryptogenic Stroke and Underlying Atrial Fibrillation) and EMBRACE) Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event) trials. ICM: insertable cardiac monitor.

(24-hour Holter monitoring or event recorder).[12] The CRYSTAL-AF trial detected AF in 8.9%, 12.4%, and 30.0% of patients who were monitored utilizing ICM at 6, 12, and 36 months compared to 1.4%, 2.0%, and 3.0% of patients who were monitored using conventional ECG monitoring, 24-hour Holter monitoring or event recorder as seen in figure 1A.[12,13] The median time of AF detection at 12 months was 84 days where the majority of these AF were asymptomatic. At 36 months, ICM has a ten times higher ability to detect AF compared to conventional ECG monitoring (30% vs 3% for ICM and conventional ECG, respectively).

On the other hand, the EMBRACE trial comprised of 572 patients with cryptogenic stroke were monitored either using a 30-day event trigger cardiac monitor or a 24-hour cardiac monitor.[9] The EMBRACE trial was able to detect AF in 16.1% of patients who used a 30-day cardiac event monitor compared to 3.2% of patients who used a 24-hour Holter monitor within 90 days. A third of the episodes had a very brief duration as seen in figure 1B.[9,13]

Accordingly, the 2020 ESC guidelines for the diagnosis and management of atrial fibrillation recommend prolonging ECG monitoring using non-invasive cardiac monitors or ICM for patients with a higher risk of developing AF. Those patients are elderly, patients with cryptogenic stroke and suggestive embolic stroke, patients with cardiovascular comorbidities, suspected LA remodeling, and high C2HEST score (a clinical risk score for predicting incident of AF in Asian subjects).[14]

Systematic vs opportunistic screening for AF

In addition to the above data that longer cardiac rhythm monitoring will yield a higher chance to detect AF, there are several rationales to do AF screening: 1) many patients with AF were asymptomatic. Data from the OneAF registry showed that ~30% of AF patients who visited the hospital were asymptomatic[11] 2) stroke with AF is more severe and has a higher permanent disability, 3) up to one-third of patients with ischemic stroke had underlying AF, and 4) a significant proportion of patients with stroke (~20%) has AF for the first time.

There are two methods of AF screening, i.e. systematic or opportunistic screening. When the patients/population were invited to go to a health care facility for AF screening is called systematic screening, whereas when the patients were screened during a routine consultation is an opportunistic screening. The Canadian Cardiovascular Society and the European Society of Cardiology recommend opportunistic screening using pulse palpation or rhythm-based devices, especially for patients ≥65 years of age. The systematic screening was recommended in patients >75 years or with high stroke risk.[14]

Pulse palpation was recommended in ESC Guideline as a Class I indication for screening of people ≥65 years of age.[14] Although less specific, this method of

screening has reasonable sensitivity for AF screening. It is therefore useful for ruling out atrial fibrillation.[15]

Digital Health Tools for Atrial Fibrillation Monitoring

The field of digital health has evolved rapidly, bringing transformation into the management of atrial fibrillation. Digital health tools have revolutionized health screening as information can be collected more frequently, increasing the reliability, validity, and ability to detect changes over time. Furthermore, traditional monitors may be ineffective in some cases as duration and time of wear may be incongruent with symptoms.[16] Thus, digital health tools will aid more ad-hoc monitoring. However, the disadvantages that come with these tools are false-positive episodes of AF due to substantial electrical or motion artifact, misclassified rhythms, and unavailability of other arrhythmias classification.[17]

Currently, there are several types of digital health tools available for monitoring, which can be divided into ECG tracing technologies and non-ECG tracing technologies. Handheld devices, smartwatch ECG, and smartphone ECG devices are some examples of ECG tracing technologies while photoplethysmography, oscillometry, and mechanocardiography are some examples of non-ECG tracing technologies.

The current screening paradigm for AF has shifted to only high-risk patients or patients with CS, intending to prevent serious complications. A multicentre, open-label randomized trial by Koh et al.[18] showed 30-day smartphone electrocardiogram monitoring considerably improve AF detection rate in patients with cryptogenic stroke. From 2017 to 2020, the trial observed the diagnostic yield of smartphone ECG recording in cryptogenic stroke patients age 55 years or older without prior history of AF. Participants were randomized in a 1:1 ratio to undergo 30 days ECG monitoring using KardiaMobile recording or additional 24 hour Holter monitoring. Participants in the intervention arm had to monitor their ECG three times a day or when they experienced palpitations. They also had to write down their symptoms and ECG monitoring using a diary. At the end of the monitoring, a blinded electrophysiologist reviewed the ECG recording and the diary. AF was detected 9.5% in the intervention arm and 2% in the control arm with an absolute difference of 7.5% and P = 0.024. The number needed to screen for AF detection was 13. As the detection improve, the number of patients taking oral anticoagulants at three months also increased significantly.

As for screening the general population, the ECG generated from digital health tools is still considered pre-diagnostic. Therefore, verification from the treating physician is needed to prevent overtreatment.[17] The Apple Heart Study is a good example to show that the probability of irregular pulse notification was low in the general population.[19] From 2017 to 2018, the trial observed the identification of AF through a smartwatch application during typical use. Participants were subjects without prior history of AF or who currently do not use oral anticoagulation. If the algorithm identified possible AF, then participants will be scheduled for a telemedicine visit and monitoring using an ECG patch. The study found that 34% of participants who received notification of an irregular pulse had atrial fibrillation on subsequent ECG patch readings with a positive predictive value of 0.8. Nonetheless, the integration of digital health technologies and health care professionals may lead to a bigger value and better care.

Conclusion

Atrial fibrillation is one of the important etiology behind the cryptogenic stroke. Pulse palpation and 12-lead ECG were recommended for AF screening in the high-risk population. A higher detection rate of AF can be achieved with a longer duration of monitoring such as insertable cardiac monitoring and 7- or 21-days Holter monitoring. Lastly, the usage of digital health tools has revolutionized the screening of AF but may generate false-positive rhythm, hence verification is needed to confirm the rhythm.

Conflict of interest

The authors report no conflicts of interest

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Ethical Clearance

Not applicable

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Review Article

Cryptogenic Stroke: A Challenge in Diagnosis and Management

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Abstract

Ischemic stroke is responsible for 85% of all stroke globally. However, the etiology of around a quarter of ischemic stroke are undetermined, this is called cryptogenic stroke. This kind of stroke affects younger population. Several mechanism are associated with the incidence of cryptogenic stroke such as paroxysmal atrial fibrillation, patent foramen ovale, atherosclerosis, and atrial cardiopathy. Despite many advanced knowledge on stroke generally, cryptogenic stroke is still a challenge in clinical settings. To understand more about cryptogenic stroke, a new term of embolic strokes of undetermined source (ESUS) is proposed and may need a specific workup. Specific workup aims to detect any silent risk factors and also to evaluate the cardiac structure. The term of ESUS also leads to the understanding that cryptogenic stroke is highly related to embolic mechanism and anticoagulation administration might benefit the patients. However, the result of several recent studies showed that anticoagulant was not superior to antiplatelet, and antiplatelet is still the preferred treatment. Studies on PFO closure also shows different result, but the majority of the trials showed benefit of PFO closure in reducing the risk of stroke recurrence.

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Keywords: cryptogenic stroke, diagnostic workup, management strategy, mechanism.

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Introduction and Definition

Stroke remains a serious condition due to impairment of cerebral perfusion and remain a global burden. Stroke can be categorized as ischemic and hemorrhagic. Ischemic stroke accounts for 85% of all stroke incidence.[1] However, despite the advanced knowledge on ischemic stroke, there is a type of ischemic stroke which the etiology can not be identified. This type of stroke is known as cryptogenic stroke. However, the term cryptogenic stroke is lack of specificity. Trial of Org 10172 in Acute Stroke Treatment (TOAST) is one of several classifications for stroke. TOAST defined cryptogenic stroke as a stroke which the cause is undetermined (not related to large artery atherosclerosis, cardioembolism, small vessel disease), the presence of two or more possible causes, or due to incomplete evaluation of the etiology.[2] Another classification of stroke, Causative Classification of Stroke System (CCS), divides stroke into 5 subtypes: supra-aortic large artery atherosclerosis, cardioembolism, small artery occlusion, other uncommon causes, and also undetermined causes.[3] The CCS classifies cryptogenic stroke as undetermined causes (this group is divided into cryptogenic embolism, other cryptogenic, incomplete evaluation, and unclassified).[4] Lastly, ASCOD classification classifies stroke based on the etiology. ASCOD stands for atherosclerosis, small vessel disease, cardiac, other, and dissection.5 Cryptogenic stroke is included into 'other' because ASCOD classification has no other categories that can describe cryptogenic stroke. These 3 classification have a different perspective on defining cryptogenic stroke. However, there are similarities in that the diagnosis of cryptogenic stroke is a diagnosis of exclusion, which other well-known etiologies have been excluded. The differences between these three classifications raises concern about the establishment of cryptogenic stroke diagnosis because both patients who underwent a minimal or limited diagnostic testing and patients who had an extensive testing then had normal evaluation will be classified as cryptogenic stroke.

Cryptogenic stroke is very related to embolic mechanism. Therefore, a new term to define cryptogenic stroke has been described. Cyptogenic Stroke/ESUS International Working Group has offered this new term called embolic strokes of undetermined source (ESUS).[6] This new term sought to define cryptogenic stroke clearly, based on the diagnostic criteria: a non-lacunar stroke without evidence of more than 50% proximal arterial stenosis (intra- and extracranial) or cardioembolic sources (paroxysmal atrial fibrillation, atrial flutter, thrombus, tumor, valve disease). Patients need to undergo several evaluation using brain computed tomography (CT) or magnetic resonance imaging (MRI), electrocardiography (ECG), echocardiography, Holter monitoring.[6] Apart from its new term of ESUS, management using anticoagulants such as dabigatran and rivaroxaban showed no benefit compared to antiplatelet in reducing stroke of undetermined source reccurence.[7,8] The purpose of this review is to discuss recent findings related to the evolving concept, diagnosis and management of cryptogenic stroke.

Epidemiology

Generally, the incidence of cryptogenic stroke is around 10-40% of ischemic stroke events. This percentage is getting lower through the years as a more advanced diagnostic modalities were done for evaluation.[9-11] In United States, cryptogenic stroke affects around 25% of all patients with ischemic stroke (180.000 people) each year.[6] The incidence of cryptogenic stroke is higher in younger population. Presence of vascular risk factors also decrease the likelihood of cryptogenic stroke. A stroke registry in Helsinki showed a decreased incidence of undetermined source stroke from >60% to around 25% in patients aged 15-19 years old and 45-49 years old, respectively.[12]

Potential Mechanism and Diagnostic Workup

Atrial fibrillation

Atrial fibrillation (AF) is a well-known etiology for stroke. However, paroxysmal and asymptomatic AF make it hard for clinician to detect the presence of AF in patients with cryptogenic stroke. ECG evaluation during the first 3 days of stroke onset and 24-hour Holter monitoring should be done as the first evaluation strategy. However, a prolonged heart rhythm monitoring might be needed after an event of cryptogenic stroke to prevent the stroke recurrence. There are 2 trials that studied about prolonged cardiac monitoring gave a beneficial impact in detect AF. EMBRACE trial, a

multi-center study, divided patients with cryptogenic stroke or transient ischemic attack (TIA) into two groups, usual care using 1-day Holter monitoring and 30-day outpatient monitoring. The primary outcome was 30 seconds of AF. This trial showed that detection of AF was higher in patient who had 30-day cardiac monitoring compared to 1-day monitoring, 16.1% and 3.2% respectively.[13] The other trial, CRYSTAL-AF, compared patients with cryptogenic stroke or TIA with usual care (ECG and inpatient monitoring) vs. group of patients who underwent a longer cardiac monitoring using insertable cardiac monitor (ICM). The primary outcome was first detection of AF >30 seconds within 6 months. The result of this study showed that detection of AF at 6 months was higher in ICM patients versus usual care group (8.9% vs 1.4%, hazard ratio [HR] 6.4; 95% confidence interval [CI], $p < 0.001$).[14] These results show that long-term rhythm monitoring in outpatient setting is beneficial in detecting AF, especially in patients after first cryptogenic stroke event. Another prospective study by Jofrida et al. also suggested that long-term rhythm monitoring was able to detect as many as 46% asymptomatic atrial fibrillation in patients with cryptogenic stroke with risk factors for AF but no history of arrhythmia.[15] This study showed a higher AF detection compared to EMBRACE and CRYSTAL-AF study. This might be due to the difference in the duration of AF being monitored (>5 minutes vs >30 seconds). To date, there is no consensus on the optimal AF duration that should be monitored to be clinically significant.

PFO

Patent foramen ovale (PFO) is a congenital abnormality of the heart that is related to an occurrence of cryptogenic stroke. PFO is a potential source of emboli due to thrombus formation. Paradoxical embolism may also occur in PFO. This happens when thrombus originating from venous system circulate through systemic circulation to the arterial system through the presence of right-to-left shunt.[16] The prevalence of PFO is higher in populations with cryptogenic stroke than normal subjects. It is also suggested to be an important risk factor of cryptogenic stroke, especially in younger population.[17] The prevalence of PFO in patients with cryptogenic stroke is around 40%. The probability of finding PFO in cryptogenic stroke is almost 3 times higher compared to control subjects (stroke with established etiology).[18] To diagnose the presence of PFO, patients will be examined using transthoracic echocardiogram (TTE) with high-specificity for PFO. During examination, patients will be asked to perform valsalva maneuver and we can find an agitated saline bubbles to the left atrium within 3 cardiac cycles.[19,20] TTE detects less PFO compared to transoesophagal echocardiogram (TEE). TEE is also the preferred method because it is better than TTE in evaluating the morphology of the shunt.[16] Suspicion of PFO in patients with negative bubble study from TTE examination might lead to additional examination using TEE. However, examination using TEE makes it difficult for the patient to perform valsalva maneuver. If patients are not eligible to undergo TEE and TTE examination result is not conclusive, transcranial Doppler ultrasonography might be used.[21] Though PFO is quite common found in stroke events, it is still a challenge to determine wether PFO is incidental or stroke-related. To overcome this challenge, a tool consists of 6 variables related to PFO can be used to determine the probability of PFO to be associated with stroke. The Risk of Paradoxical Embolism (ROPE) consist of variables about the presence of risk factors and age. Patients with ROPE scores 7-10 have high likelihood of PFO-related stroke.[22]

Atrial cardiopathy

The term of atrial cardiopathy arises because there is conflicting findings on subclinical AF as an embolic source. Although AF is highly associated with thrombus formation, a study showed no association between subclinical AF and embolic events.[23] Atrial cardiopathy can be diagnosed based on the ECG appearance, imaging, and also biomarker levels. ECG examination will show P wave terminal force in V1. The biomarker measured to diagnose atrial cardiopathy is NT-proBNP (N-terminal pro-B-type natriuretic peptide).[24] Atrial fibrosis increases the risk of stroke. In a study using magnetic resonance imaging (MRI) to evaluate atrial structure, atrial fibrosis was found more prevalent in group of patients with cryptogenic stroke. In this study, percentage of atrial fibrosis was comparable in patients with AF and undetermined source of stroke.[25]

Atherosclerosis

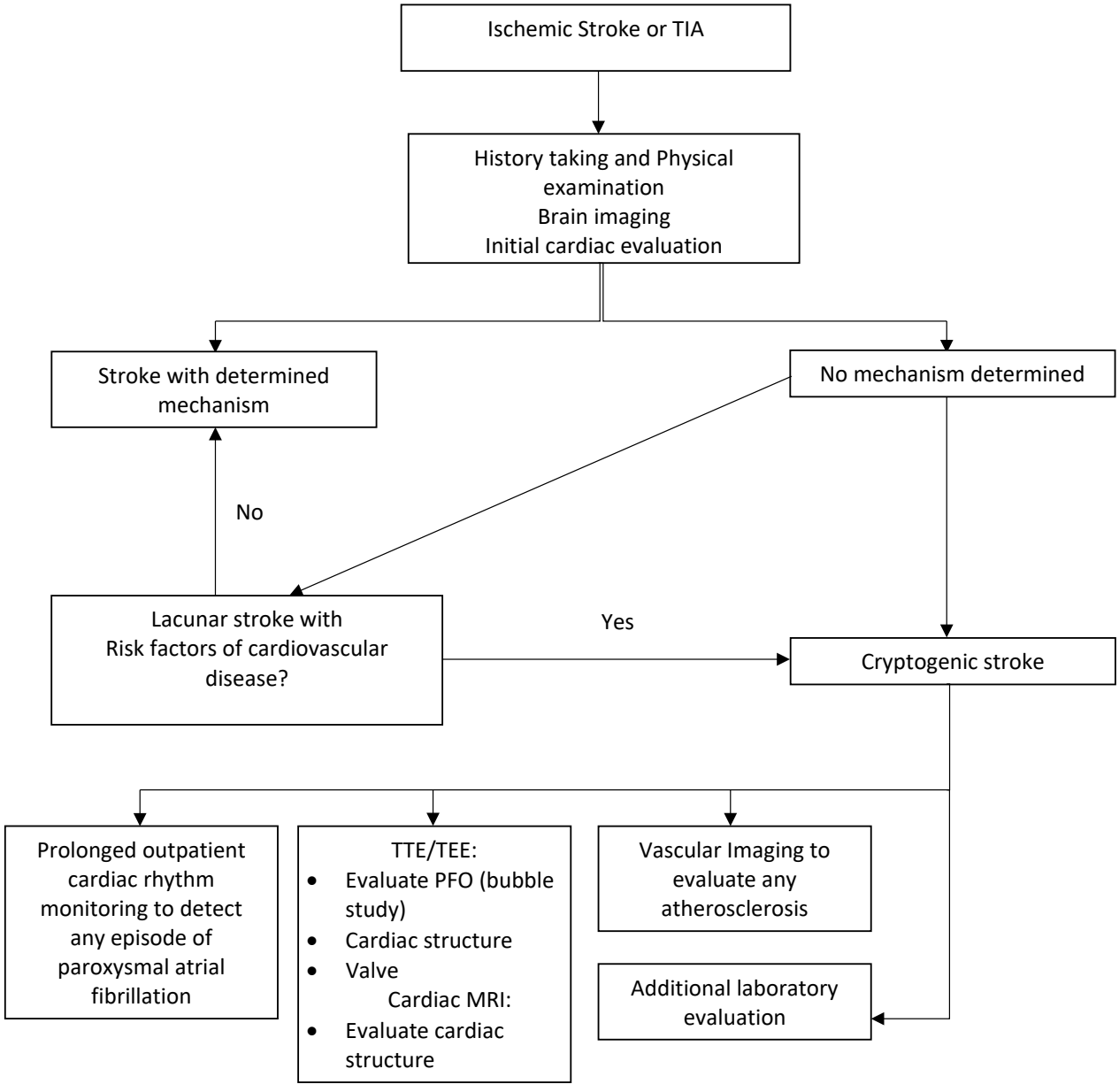

Figure 1. Proposed diagnostic algorithm for cryptogenic stroke.

Atherosclerotic plaque is a potential etiology for ischemic stroke. In cryptogenic stroke, substenotic atherosclerotic plaque also has a role due to plaque rupture and artery-to-artery embolization. In a study by Gupta et al., it was showed that in 22% of patients with cryptogenic stroke, evidence of intraplaque haemorrhage was found and became the underlying mechanism of cryptogenic stroke. This study used magnetic resonance angiography (MRA) to evaluate the plaque. The plaque was also found ipsilateral to the infarct.[26] Aortic arch atherosclerosis (AAA) is suggested to be a risk factor for cryptogenic stroke. A mobile complex plaque with size of 4mm increases the risk of embolism.[27,28] Detail evaluation of AAA is essential to determine the extent of the lesion. Examination using TEE can give a detail information on morphology of the plaque and also the location.[29] A less invasive yet reliable modality such as computerized tomography angiography (CTA)

Table 1. Trials Comparing PFO Closure and Medical therapy.

Name	Result	Value	Result	Result
CLOSURE[31]	Percutaneous closure device	Aspirin, warfarin, or both	Stroke or TIA in 2 years	No benefit of PFO closure, stroke or TIA recurrence is 5.5% vs 6.8% in PFO closure group and medical therapy group respectively (p=0.37)
PC[32]	Percutaneous closure device	Any antithrombotic	Stroke, TIA, peripheral embolism, or death	No benefit of closure compared to medical treatment.
GORE-REDUCE[33]	Percutaneous closure	antiplatelet	stroke recurrence	Stroke recurrence in PFO vs medical therapy: 1.4% vs 5.5% (p<0.04)
RESPECT[34]	Percutaneous closure	Aspirin, clopidogrel, warfarin, or aspirin/ dipyiridamole	Stroke or death	Stroke recurrence in PFO vs medical therapy: 3.6% vs 5.8% (p=0.046)
CLOSE[35]	Percutaneous closure	Antiplatelet or anticoagulant	Stroke recurrence	No patients in PFO closure group had stroke recurrence. 14 patients in antiplatelet group had recurrence of stroke
DEFENSE-PFO[36]	Percutaneous closure	Any antithrombotic agent	Stroke, death, or major bleeding.	No patients reached the primary endpoint in PFO closure group compared to medical therapy group (12.9%)

or MRI can also be done, especially, these modalities give additional information on the other parts of aorta (descending and abdominal aorta).[30]

Treatment

Management of stroke is essential to prevent recurrence. This includes controlling the risk factor. Antithrombotic therapy using antiplatelet has been and still the treatment of choice for cryptogenic stroke patients. Given that cryptogenic stroke is associated with embolic mechanism, administration of anticoagulant may be beneficial. Several studies have studied the comparison between some anticoagulant and antiplatelet in managing cryptogenic stroke. NAVIGATE-ESUS and RESPECT-ESUS are two trials that compared the use of novel oral anticoagulant to antiplatelet.[7,8] Both these studies showed that rivaroxaban and dabigatran were not superior to aspirin in preventing stroke recurrence. In NAVIGATE-ESUS trial, rivaroxaban and aspirin had a comparable incidence of stroke recurrence (5.1% vs 4.8%, p=0.52). Administration of rivaroxaban even increased the risk of major bleeding compared to aspirin (1.8% vs 0.7%, p<0.001).[7] The same result was also showed by RESPECT-ESUS trial. Dabigatran did have a lower incidence of stroke recurrence, however it was not significant compared to aspirin (4.1% vs 4.8%, p=0.10). Dabigatran also increased the rsk of major bleeding (1.7%) compared to aspirin (1.4%).[8] Patients with PFO however might need a more invasive management strategy, a closure of PFO using percutaneous or open technique. There has been several clinical trials about percutaneous closure of PFO and its benefit in preventing stroke recurrence. These trials compared PFO closure vs optimal medical therapy. The result of these studies are presented in Table 1. While there are conflicting result, most of the studies reported that PFO closure was beneficial than medical therapy alone in preventing stroke recurrence.[31-36] The standard treatment for substenotic atherpsclerosis includes antiplatelet therapy, statin, and risk factor modification. Intervention management such as stenting or endarterectomy is not necessary in this group of patients unless, optimal medical therapy does not prevent the recurrence of stroke.[24]

Discussion

Cryptogenic stroke is still a challenge due its heterogenous concept and definition. While studies on cryptogenic stroke is still on going, stroke recurrence prevention strategy must be done based on current data. It is important to order a prolonged outpatient monitoring of cardiac rhythm instead of inpatient monitoring only. The optimal duration for heart rhythm monitoring is not known yet, but a longer duration are associated with increased detection of AF. However, it is recommended to monitor cardiac rhythm for at least 30 days. If no AF detected, a longer monitoring should be considered.[37] A recent meta-analysis on optimal duration for prolonged cardiac monitoring also supported a longer term heart rhythm monitoring using implantable cardiac monitor (ICM) for patients with suspicion of cryptogenic stroke with initial negative result of AF. The result showed that longer term ICM duration (<6 months, ≥6 and ≤12 months, > 12 and ≤24 months, > 34 months) was associated with an increased AF detection rates.[38] While several recent studies on anticoagulant showed no significant benefit when compared to aspirin, the result from ongoing studies, ARCADIA and ATTICUS trial might give a clearer evidence for anticoagulant administration.[39,40]

Conclusion

Cryptogenic stroke is still a challenge and many studies have given more knowledge for us physician. The goal of cryptogenic stroke management is to prevent the stroke recurrence. Patients with suspicion of cryptogenic stroke must be evaluated thoroughly. A prolonged cardiac monitoring in the outpatient setting is recommended to increase AF detection. Other examination such as cardiac imaging are also important to determine any cardiac structure abnormalities, especially right-to-left shunt. This is important to decide whether invasive management is needed. Studies on management strategy are still underway for us to give a proper treatment. Management given to the patients aims to control the risk factor.

Conflict of Interest

None to be declared

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Review Article

Patent Foramen Ovale and Cryptogenic Stroke : Challenges in Diagnosis and Management

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Abstract

A patent foramen ovale (PFO) is a common disorder that affects between 20-34% of the adult population. This condition is a benign finding for most people. However, In some the PFO can open widely and enabling paradoxical embolism to transit from venous to arterial circulation, which is associated with stroke and systemic embolization. There are still unclear to date regarding the effectiveness of pharmacological anticoagulant therapy, defined as antithrombin or antiplatelet therapy, which has proven to be more beneficial for patients with PFO and cryptogenic stroke. In addition, surgical and transcutaneous PFO closure has been proposed for secondary prevention of stroke in patients with cryptogenic stroke with PFO. Both catheter-based and surgical modes of closure have been shown to reduce the incidence of subsequent embolism substantially. This review will discuss the evidence regarding the relationship between PFO and cryptogenic stroke and decision making for management strategies.

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Keywords: Patent Foramen Ovale, Cryptogenic Stroke, Paradoxical Embolism, Echocardiography, Device Closure.

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Introdution

The Patent foramen ovale (PFO), a part of the disorder known as an atrial septal defect, is a remnant of normal fetal anatomy. More than half of babies will develop PFO by six months of age.[1] Although it has no clinically significant impairment, it can persist into adulthood. For most people, PFO will remain undetected or appear only as an accidental discovery during a cardiac examination. However, some PFOs may be wide open and act as access for materials such as thrombus, air or vasoactive peptides to provide shunt from the veins to the arterial circulation - paradoxical embolism. This is associated with cryptogenic (having no other identifiable cause) stroke, systemic embolism, migraine with aura, acute limb ischemia due to embolism and decompression sickness in divers.[2,3]

The diameter of the PFO (average, 4.9 mm) allows passage of a sufficiently large embolism from the venous system to occlude the middle cerebral artery to reach the cerebral circulation. Worldwide annually, 345,000 patients aged 18-60 years present with PFO and embolic stroke from undetermined sources. Young patients with cryptogenic stroke had a 2.3-fold increased relative risk of having a PFO, compared with individuals of the same age with a clear cause of stroke, suggesting that PFO is the causative mechanism of stroke in these patients.[4]

Based on transesophageal echocardiographic (TEE) screening , patients with cryptogenic stroke / transient ischemic attack (TIA) had a mean prevalence of any PFO, PFO associated with atrial septal aneurysm (ASA), and large PFO of 43.2%, 14.5%, and 19.5%, respectively. The prevalence of any PFO, PFO with septal aneurysm, and large PFO showed a noticable variability between younger patients (<50 years) versus older patients: 59.9% vs 35.2%, 16.3% vs 11.6 %, and 18.6% vs. 22.9%, respectively; indicating that PFOs tend to close over time, large PFOs tend to persist into older age.[5]

PFO – Associated Clinical Syndrome

Cryptogenic stroke

PFO is a flap-like opening between the atrial septum secundum and primum at the fossa ovalis. this opening serves as a track for blood to the systemic circulation during the womb. as pulmonary circulation increases after birth, the PFO functionally begins to close. Complete closure of the anatomical PFO usually occurs in about 12 months. PFO plays a role in increasing the risk of stroke from paradoxical embolism. The risk of cryptogenic stroke is increased in PFO with larger defects and the presence of interatrial aneurysms, this may be due to increased in situ thrombus formation in the aneurysm tissue or because PFOs with interatrial septal aneurysms tend to have larger defects. Despite previous reports noticing paradoxical embolism via PFO, this phenomenon as a risk factor for stroke remains difficult to prove because deep venous thrombosis was rarely detected in such patients. In one study, pelvic vein thrombus was found to be more frequent in young patients with cryptogenic stroke than in those with known the cause of stroke. These findings may serve the source of venous thrombi, particularly when the source of venous thromboembolism (VTE) was not identified.[2]

The relationship between PFO and cryptogenic stroke has been introduced in the 80s of the last century. Paradoxical embolism is the suspected mechanism that occured in PFO with stroke when a thrombus from the systemic venous circulation passes through to the systemic circulation via a right-to-left shunt. The concept of paradoxical embolism via PFO was first conceived by Zahn in 1881, who discovered a thrombus from a uterine vein trapped in PFO on postmortem examination. In patients with cryptogenic stroke, the rates of PFO (59% vs 19%) and deep vein thrombosis (20% vs 4%) were higher than patients with a stroke of known cause.[5,6] In addition to paradoxical embolism, the combination of large PFO with and atrial septal aneurysm (ASA) has been suggested as a cause of left atrial (LA) dysfunction predisposing to systemic thromboembolism that normalized after PFO device closure.[5]

About 40% of ischemic strokes have no clear etiology and are therefore termed cryptogenic. A study conducted on 60 adult patients under 55 years with ischemic stroke compared contrast echocardiography with 100 normal subjects. The prevalence of PFO was significantly higher in the stroke group (40%) than in the control group (10%) (p 0.001). The study concluded that PFO-induced paradoxical embolism is the cause of stroke.7 The PFO-ASA study supports these findings,

in which 46% of young cryptogenic stroke patients had PFO.8 Cramer et al.[6] evaluated young stroke patients (ages 18 to 60 years) immediately after the onset of stroke using magnetic resonance imaging (MRI) venography. Pelvic deep vein thrombosis was increased in the cryptogenic stroke population compared with controls (20% vs 4%). The cryptogenic stroke group was younger (42 vs 49 years). The prevalence of PFO was significantly higher in the cryptogenic stroke group than in the control group (59% vs 19%). A prospective study of 598 patients (ages 18 to 55 years) who had a cryptogenic stroke showed that 36% had PFO, 1.7% had ASA, and 8.5% had both condition. Patients with PFO and ASA who have had a stroke have a higher risk of having recurrent strokes.[9]

An association between prothrombotic conditions and PFO with cryptogenic stroke has been reported. Factor V Leiden and prothrombin G20210A mutations were observed to occur more frequently in patients with PFO and cryptogenic stroke.[10,11] In one study, at least one of these two prothrombotic genotypes was significantly higher in young cryptogenic stroke patients than in age-matched controls (10.3% vs. 2.5%; p = 0.008), with the prothrombin G20210A mutation significantly higher than factor V Leiden (8.2% vs 2.1%).[12] The association between either this two genotypes and PFO increased the risk of stroke by 4.7-fold. The association between PFO size and the presence of antiphospholipid antibodies has been reported.[13] Common risk factors for venous thrombosis, such as recent surgery, traumatic injury, or use of contraceptive drugs, may increase the risk of paradoxical embolization via PFO.[14]

Platypnea - Orthodexia syndrome

Platypnea-orthodeoxia syndrome consists of dyspnea and desaturation of the artery in an upright position (platypnea) with restoration in the supine position (orthodeoxia). The two components must coexist to establish this syndrome. One of the causes is an anatomical defect and the other is functional. The anatomical component must have an interatrial shunt, consist of an atrial septal defect (ASD), PFO, fenestrated ASA, or an intrapulmonary shunt.[15,16]

In this syndrome there is an increase in right atrial pressure which causes a right-to-left shunt. Interestingly, blood can flow from right to left at the atrial level even when the right heart pressure is normal, as is usually the case with persistent eustachian valves. The definitive treatment for platypnea-orthodeoxia is closure of the atrial shunt.[15,17]

Decompression Sickness

Arterial gas embolism via ASD was first reported in scuba divers in 1986.[18] Type 1 DCS consists of local joint pain, musculoskeletal pain, and / or skin rash, and type 2 DCS consists of neurological symptoms (tingling of the legs, paresthesias, severe headache with altered mental status, paraplegia, loss of consciousness, audiovestibular symptoms, and dyspnea with chest pain). PFO is significantly associated with type 2 DCS.[15]

A recent study found a strong association between PFO sizes and DCS in 230 divers.[19] Another study demonstrated the functional and anatomical characteristics of PFO with and without DCS, this study shows that DCS is associated with right-to-left shunting at rest. Atrial septal mobility and PFO diameter are also associated with the risk of DCS.[20]

Migraine

Migraine and vascular headaches are associated with PFO. Migraine headache is a benign headache syndrome that recurs, accompanied by nausea, vomiting, and / or other symptoms of neurological dysfunction. More than 2,500,000 patients in the U.S. experiencing at least one migraine headache each week, with a lifetime prevalence of about 18%. Migraine is a risk factor for cryptogenic stroke, notably in young patients without atherosclerotic risk factors. [15]

One study represented a significant association between PFO closure and migraine improvement with aura using the Transcranial Droppler (TCD). In that study, 5 of 17 patients experience complete resolution of migraine, 10 of 17 patients admit improvement, and 2 patients had no change for 6 months after closure of the PFO.21 Another study conducted to find the association between PFO and migraine with or without aura. The prevalence of PFO was 48% in patients with migraine, 23% in patients without migraine, and 20% in the control group. The differences between patients with and without migraine and PFO were striking, as were the differences between patients with aura and the control group. However, the group without aura had no difference in PFO prevaence compared to the control

group. A recent study showed transcatheter PFO closure led to complete resolution or a marked reduction in migraine frequency.[22] In this study, has been investigated 162 patients with paradoxical brain embolism who underwent transcatheter PFO closure. Complete migraine resolution occurred in 56% of patients, and 14% of patients reported a significant reduction in migraine frequency. Patients reported a decrease in the mean number of migraine episodes per month by 80% after PFO closure (6.8 ± 9.6 before closure vs 1.4 ± 3.4 after closure, $p < 0.001$). Another study also concluded that PFO or ASD closure in patients with migraine headaches exhibit to migraine resolution or improvement about 76% of 89 adult patients.[23]

Venous blood can enter the arterial circulation directly without passing through the pulmonary circulation via the PFO. Some chemicals and hormones such as serotonin can pass through the pulmonary circulation and directly cross the blood-brain barrier causing migraines.[24] Normally, Serotonin produced from platelet aggregation. Other evidence suggests that platelet activation and aggregation have been shown to increase in migraine patients.[25] In addition, a study showed that aspirin, an anti-platelet drug can reduce platelet-fibrin complex formation and expexted to improve migraine, also has a statistically significant prophylactic effect on migraine.[26]

In addition, a small embolism from the systemic circulation can pass via PFO and directly into the arterial system. This paradoxical embolism can cause tiny brain infarction, developoing low perfusion or cortical spreading depression, thereby leading to migraine attacks.[24]

Diagnosis

Most patients with an isolated PFO have no symptoms. For the majority of people, the PFO will remain undetected or accidentally discovered during a heart exam. When PFO do accure, the patient may have a history of stroke or transient ischemic attack of undetermined etiology (cryptogenic stroke), migraine, neurologic decompression sickness (seen in PFO experienced by a small percentage of scuba divers).[3]

Some imaging modalities can be used to detect PFO, especially transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), or transcranial Doppler ultrasound (TCD).[4] TTE is a non-invasive examination to detect PFO.[27] TTE is the least sensitive, detecting only 50% to 60% of the PFOs found in TEE or TCD. When compared with autopsy which is the gold standard diagnosis, TEE has a sensitivity of up to 90% and a specificity above 95%. TCD can detect 100% of the PFO found in TEE and detect 10% of the PFO that is missed with TEE; TCD can even detect small PFOs that missed with TEE by perform Valsalva maneuver, and confirmed the waveforms formed during TDC. TEE and TCD are complementary. Both can detect PFO and quantify the shunt size. TEE also able to characterizes PFO anatomy and presence of an atrial septal aneurysm (ASA) and assesses the presence of competing proximal sources of embolism, including aortic arch atherosclerosis, atrial appendage thrombi, and signs of atrial cardiopathy. TCD uniquely quantifies the cerebral burden of paradoxical embolism, on both bubble study and during 30 minutes of monitoring for spontaneous microembolism, and assesses the presence of competing distal arterial sources of embolism.[4]

TTE and TEE have a considerable clinical role in patients with PFO and cryptogenic stroke, however, the selection of these echocardiographic modalities should be made on a case-by-case basis. A study in ischemic stroke patients with unknown etiology (before getting an echocardiogram) evaluated patients with TTE and TEE.28 Based on the TEE results, the presence of PFO was determined the saline bubble shunting into the left atrium in three cardiac cycles (small shunt 3-10 bubbles , moderate 10-20 bubbles and large> 20 bubbles), often augmented by the Valsalva maneuver that triggers the bubble to pass by increasing right atrial pressure. However due to the low sensitivity of TTE for PFO detection, a high suspicion for PFO with a negative TTE will often lead to ordering a TEE. Although the TEE shows a better look at cardiac structures, it is semi-invasive, with sedation that often limits or precludes the Valsalva manoeuver.[27] These suggest that TEE may be superior to TTE in including or excluding a cardioembolic source for stroke; on other hand, they suggest that when a stroke etiology has not been identified using conventional means, a TEE should be considered to help identify the stroke etiology and guide stroke prevention strategies.[28]

TCD has been shown to be more sensitive than TEE and just as specific as TTE or TEE in emboli detection. But TCDs cannot detect additional and potentially

relevant structural features such as ASA and septal mobility (features that affect shunt size characterization) nor really distinguish between intracardiac and intrapulmonary shunts such as pulmonary arteriovenous malformations. ASA is present when redundant tissue in the fossa ovale causes more than 10–15mm of bulging into the left or right atrium during respiration, and may indicate a greater recurrent stroke risk compared with PFO alone. Tobe et al found that a shunt grade determined by TCD can be a stronger predictor of TIA or stroke than shunt detection by TEE, and that TEE missed 15% of the shunts caught by TCD, and of those 40% were large shunts (grade 3 and higher). But, TCD should not replace echocardiographic modalities in PFO detection and other shunt features, but can be a complementary and highly sensitive modality when performed by a properly trained and experienced operator.[27]

Despite the strong evidence shows there is an association between PFO and the risk of stroke, confirming a causal relationship in a given patient is still challenging. Even in those with cryptogenic stroke, at least one third of PFOs discovered are likely to be incidental and closure of an incidental PFO would expose patients to procedural and device-related risks while leaving the actual cause of stroke unrevealed. Estimating the probability of a PFO being embolism related is based on patient's clinical profile (younger age, absence of atherosclerosis risk factors, a higher RoPE scope, pulmonary hypertension/ obstructive sleep apnea), cerebral infarct pattern (typical of embolism), anatomical PFO features (large shunt, atrial septal aneurysm), and conditions potentially predisposing to/ precipitating paradoxical embolism through PFO.[5]

Clinical profile

Worldwide, about 345,000 patients aged 18–60 years with a PFO and an embolic stroke of otherwise undetermined source preset each year. Younger patients with a cryptogenic stroke have a 2.3-fold increased relative risk of having a PFO, compared with age-matched individuals with a stroke of a clear cause, suggesting 73% likelihood that PFO is the mechanism of the stroke in those patients.[5]

Several studies have examined clinical hints that can be used to determine how likely PFO is causing paradoxical embolism. History of diseases such as pulmonary embolism or DVT, migraine, stroke symptoms preceded by the Valsalva maneuver, and symptoms of stroke / TIA coincide on waking from sleep preceded by sleep apnea has been associated as a major risk factor for cerebrovascular events associated with PFO.27 The development of atheroscelrotic plaque was linearly correlated with the incidence of ischemic stroke. However, PFO as a cause of stroke is supported by the absence of risk factors for plaque development such as younger age, absence of hypertension, hyperlipidemia, diabetes mellitus, and smoking.[4]

Table 1. The Risk of Paradoxical Embolism (RoPE) score.[29]

Name	Value
Vascular risk factors	
No Hypertension	1
No Diabetes Mellitus	1
No prior stroke or transient ischaemic attack	1
Non-smoker	1
Age	
18-29	5
30-39	4
40-49	3
50-59	2
60-69	1
≥70	0
Stroke features	
Cortical infarction	1

The difficulty in attributing PFO for the culprit cause of stroke has led to the development of the Risk of Paradoxical Embolism (RoPE) score for cryptogenic stroke, which was drawn from a database of 3023 patients with cryptogenic stroke, who had previously been examined using TEE or TCD, the cryptogenic stroke defined by the Trial. Org 10172 in Acute Stroke (TOAST).[27,29] The RoPE score is calculated from the following variables: younger age, the presence of a cortical stroke on neuro imaging, absence of diabetes, absence of hypertension, non smoker, and no prior stroke or TIA. The highest RoPE score, that indicating a higher likelyhood PFO related stroke rather than incidental, can be found in case of the youngest patient with superficial strokes and without atherosclerosis risk factors. RoPE score is helpful and practical, but should always be used in conjunction with other parameters because it is only modestly validated and does not account for high-risk morphological features of the PFO.[30] There was few external validation studies, one of small study identified

a RoPE score >7 as a cutoff point that indicated PFO is more likely to be stroke related.[31] In other cohort study of a cryptogenic stroke, the prevalence of PFO-related right-to-left shunt was 50–56% in patients with RoPE scores <7 compare with 79% in those with a score ≥7. Additionally, a higher RoPE score correlated modestly with the severity of right-to-left shunt.32 Another studies use a score >5 or >6 to classify PFO as stroke related.[33,34]

Cerebral infact pattern

Stroke was only called as cryptogenic after history, exam, routine labs and extensive testing including; initial neurovascular assessment (CT/MRI, vascular Imaging), initial cardiac assessment does not identified the stroke mechanism.[28] Association between PFO and cryptogenic stroke has been established in the 80s of the last century. Paradoxical embolism is the suggested mechanism PFO related to stroke and occurs when a thrombus from the systemic venous circulation passes to the systemic arterial circulation trhough a right-to-left shunt.[5] The mean diameter of persisting PFOs is 4.9 mm (range about 1–19 mm), more than sufficient to allow passage of emboli large enough to occlude the middle cerebral artery stem (3 mm) and major cerebral cortical branches (1 mm).[4]

Noncontrast head CT highly effective for excluding intracranial hemorrhage; however, it is poor at best for identifying small infarcts. MRI is better than CT in detecting ischemic stroke. when available, MRI should be preferred over CT for the initial imaging of the stroke patient. Diffusion-weighted found in MRI may also help identify a stroke mechanism; for example, multiple lesions in different vascular territories may suggest a cardioembolic origin. Otherwise, scattered lesions to a single vascular distribution suggest large-artery atherosclerosis. Other study have suggested that cryptogenic stroke patients who have clinical and CT evidence of one ischemic lesion should take a subsequent MRI assessment to further delineate potential causes.[35,36] The probability that stroke is related to PFO is increase in case of a cortical infarct (suggesting an embolic mechanism).[5]

Management of PFO-Related Cryptogenic Stroke

In general there are two treatment options for secondary prevention of recurrent stroke in cryptogenic ischemic stroke patients with PFO include medical treatment (alone or in combination, antiplatelet and anticoagulant therapy) and PFO closure (surgical PFO closure, and percutaneous PFO closure).[4]

Medical Treatment

Acording to pathophysiological standpoint, anticoagulation might be better than antiplatelet therapy in purpose to preventing PFO-related stroke, as anticoagulants is superior prevent thrombi arising in veins. Nevertheless, anticoagulation is also associated with increased bleeding event, and comparative studies have shown only modest evidence of an efficacy advantage.[5] In addition, bleeding complications were significantly more frequent among anticoagulated patients. Compared with older anticoagulants, non–vitamin K–dependent oral anticoagulants are promising options, more reduced bleeding rates, and comparable efficacy in prevention of DVT, but in patients with PFO have not been studied yet.[4] While antiplatelet therapy applied in clinical trials is variable, including of acetylsalicylic acid, clopidogrel, and/or extended-release dipyridamole. Currently available evidence suggests that anticoagulants may be superior to antiplatelet therapy.[5]

Among the medical therapy options, US national practice guidelines weakly endorsed antiplatelet therapy as preferred. Although physiological reasoning suggests that anticoagulation might be superior to antiplatelet therapy, as anticoagulants better avert stasis thrombi arising in veins, anticoagulation is also associated with increased bleeding, and comparative studies are only weakly suggestive of an efficacy advantage. There was two randomized trials comparing anticoagulant against antiplatelet therapy in subgroups of patients with PFOs and cryptogenic ischemic stroke found non-significant efficacy differences: PICSS trial (PFO in Cryptogenic Stroke Study; hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.16–1.67; P=0.28)[37] and CLOSE trial (Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; HR, 0.44; 95% CI, 0.11–1.48; P=0.18).[38]

PFO and deep vein thrombosis (DVT) are both common findings at the same time. Currently AHA/ASA Stroke Prevention in Patients with Stroke or TIA Guidelines recommend the following ; There are

insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO (Class IIb; Level of Evidence B). For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended. (Class I, Level of Evidence B) For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics (Class I; Level of Evidence A). When anticoagulation is contraindicated, an inferior vena cava filter is reasonable (Class IIa; Level of Evidence C).[28]

PFO Closure

Surgical closure of the PFO requiring thoracotomy and cardiopulmonary bypass is rarely performed as independent therapy. It may be an option if the patient is undergoing heart surgery for other indications. In observational series, open surgical closure has a low rate of perioperative mortality, but can leave sequelae of morbidity including AF, pericardial effusion, postoperative bleeding, infection, and postpericardiotomy syndrome. The annual incidence rate for recurrent stroke or transient ischemic attack ranges from 0% to 9%. Recurrence of cerebral ischemia associated with incomplete closure of the PFO with an open surgical approach occurs in up to 73% of patients.[4]

The percutaneous PFO closure device is a minimally invasive approach to anatomical management that has advanced in the last quarter century since the first trials were carried out on humans. Device designs differ in important ways that affectease of delivery, efficacy in achieving complete closure, and adverse effects.[4] A large number of devices with varying shapes and sizes have been marketed, the need for evidence from randomised controlled trials prior to approval means fewer devices have been approved by the Food and Drug Administration. Most devices are of double-disc design, connected by a short waist. The Gore Septal Occluder (WL Gore & Associates) and the AMPLATZER PFO Occluder (Abbott Vascular) are two of the more commonly used devices (Picture 1). The Gore Septal Occluder is constructed from five nitinol wires covered with expanded polytetrafluoroethylene, early clinical experience has shown that it is a versatile device with easy deployment, high procedural success rates and low complication rates. The AMPLATZER PFO Occluder is also a nitinol-based device. These devices are used most often in randomized controlled trials, and the evidence for their effect is very reliable. The operator must gain experience using different devices to find out the best outcome for the patient.[3]

Recent investigations have shown that closure of PFO, particularly with atrial septal aneurysms and / or large interatrial shunts, can reduce the risk of recurrent stroke compared with pharmacological treatments. However, it remains challenging to risk stratify patients with suspected PFO-associated stroke and to decide whether device closure is indicated or not.[5] Patients with cryptogenic stroke or TIA and PFO without evidence of DVT, available data do not support the benefit for PFO closure (Class III; Level of Evidence A). In PFO and DVT settings, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT (Class IIb; Level of Evidence C).[28]

The antithrombotic regimen after device closure is still uncertain.[3] Hence, routine dual antiplatelet therapy (Aspirin and clopidogrel) is recommended for 1-6 months after PFO closure, and single antiplatelet therapy (usually clopidogrel 75 mg daily) afterwards for at least 5 years.[3,5] Transthoracic echocardiography (TTE) should be performed prior to discharge and 6 weeks after device insersion to eliminate pericardial effusion and device embolisation. Potential successful rate of closure are high using modern devices, and the main objective is sealing the PFO flap valve opening. Total closure depends on device endothelialization and can take up to 6 months, after which a repeat bubble study should be performed to confirm complete closure has occurred.[3]

Conclusion

In this article, PFO management focused on cryptogenic stroke has been discussed, along with scientific evidence of either pharmacological or intervention for PFO closure. Clinical knowledge and attention to detail in indication for the procedures and risks to patients are required with the help from experienced interventional cardiologists.

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Case Reports

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Case Series Coexistence of PFO with Other Conditions: WWho's The Culprit?

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Abstract

Background: Patent foramen ovale (PFO) is a major cause of cryptogenic stroke (CS). However, it is still possible that PFO comes with those other conditions during evaluation. This paper presents a series of CS cases highly suspected due to PFO origin with each of its special presentations.

Case illustration: We present three cases of CS with PFO as a possible contributing factor. Case 1 showed a patient with repeated ischemic strokes that was investigated to be cryptogenic in origin. Case 2 showed CS with PFO and occult atrial fibrillation. Case 3 showed CS at a young age caused by a PFO with protein C/S deficiency.

Conclusion: The role of PFO as a culprit, risk factor, or a coincidental finding in CS is still debatable and is a controversial issue. Determining PFO as a cause of CS requires a thorough consideration of clinical and PFO anatomical/ morphological factors.

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Keywords: Cryptogenic Stroke, Patent Foramen Ovale, Occult Atrial Fibrillation, Thrombophilia.

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Background

Cryptogenic stroke (CS) is an ischemic stroke without apparent etiology even after adequate diagnostic evaluation.[1] 25% of all ischemic stroke cases are cryptogenic, and more than two-thirds originate from emboli. Cardiac embolism is believed to provide the most significant contribution to the occurrence of cryptogenic stroke.[2] Conditions that may cause a CS include a patent foramen ovale (PFO), aortic arch atheroma, occult paroxysmal atrial fibrillation, and inherited thrombophilias.[3]

PFO is indeed a major cause of CS, and its role as a culprit, risk factor, or a coincidental finding is questionable. The mechanism of the stroke that occurs is still uncertain.[4] This paper presents a series of CS cases highly suspected due to PFO origin with each of its special presentations.

Case Illustrations

Case 1

A 43-year-old man with a history of transient ischemic attack (TIA) presented to the emergency department with severe cephalgia for three days. One month before, he had a history that he could not control his right limb when driving the car. Physical examination and electrocardiography (ECG) were normal. He had increased triglyceride (184 mg/dL) and uric acid (7.4 mg/dL) levels. A non-contrast-enhanced magnetic resonance angiography (NC-MRA) revealed an old infarction in the parasagittal left frontal lobe (Figure 1). The transthoracic echocardiogram (TTE) was unremarkable with normal heart functions, left ventricular ejection fraction (LVEF) 70%, and no thrombus. He underwent a transesophageal echocardiogram (TEE) and showed positive bubble contrast study (Figure 2). Holter monitoring for seven days showed no atrial fibrillation. The patient received antiplatelet, anticoagulant, and statin therapy.

Six months later, the patient came to the hospital with left facial weakness and a history of mild traffic accidents. Non-contrast head CT showed no bleeding due to anticoagulant therapy administration, and no new infarction. The patient was referred for percutaneous

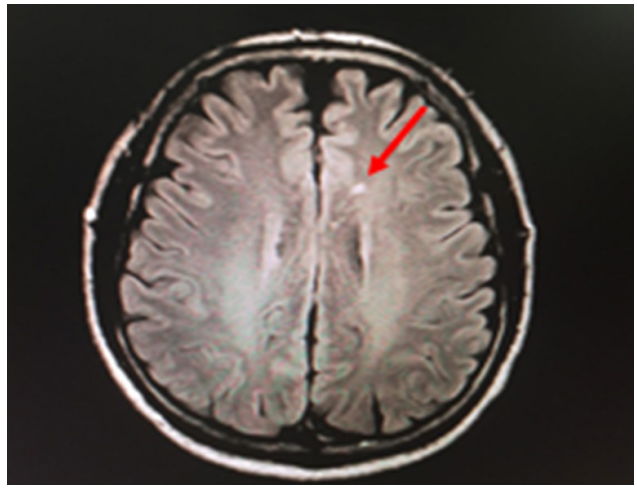

Figure 1. MRA of head showing old infarction in the parasagital left frontal lobe marked by red arrow.

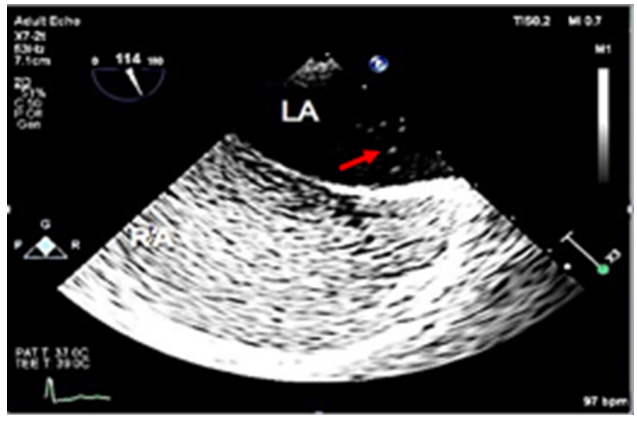

Figure 2. Bubbles (red arrow) are crossing from right atrium to left atrium through PFO

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PFO closure.

Case 2

A 53-year-old woman with a history of hypertension, dyslipidemia, and recurrent stroke came to the hospital for a medical check-up. The patient had a history of three strokes the last of which was three months ago as manifested by sudden speaking difficulties. Physical examination and ECG were normal. Lab results showed increased low-density lipoproteins (LDL) (164 mg/dL) and triglycerides (179 mg/dL). NC-MRA of the head revealed old infarctions in the right frontoparietal and left occipital area (Figure 3).

TTE showed mild aortic regurgitation with normal

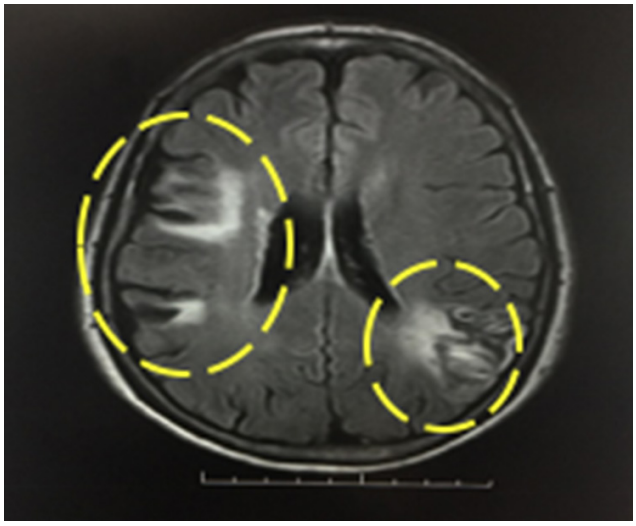

Figure 3. Multiple infarct marked by circles.

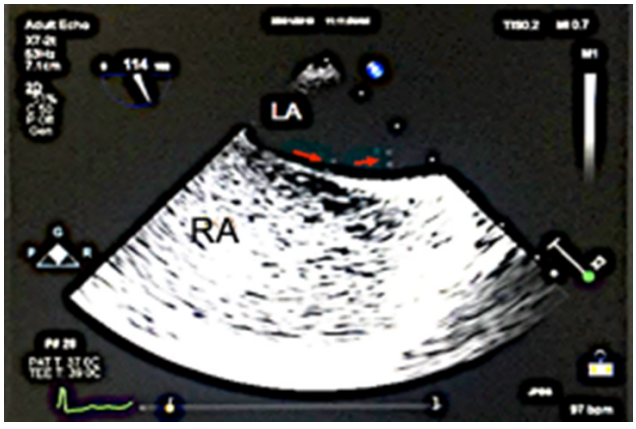

Figure 4. Bubbles (red arrow) are crossing from right atrium to left atrium through PFO

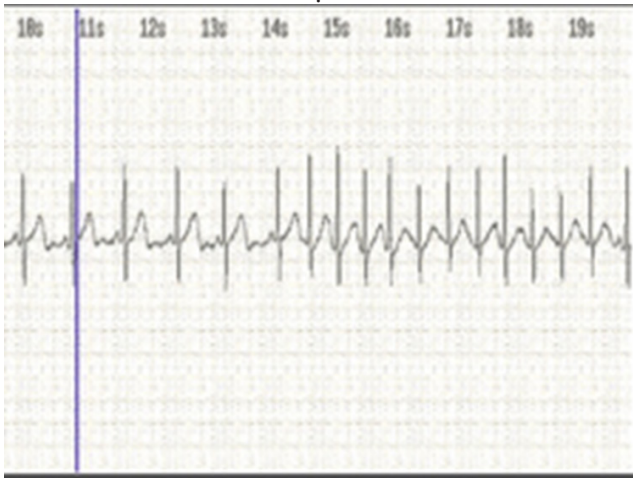

Figure 5. Occult Paroxysmal Atrial Fibrillation showed in 7d-Holter monitoring.

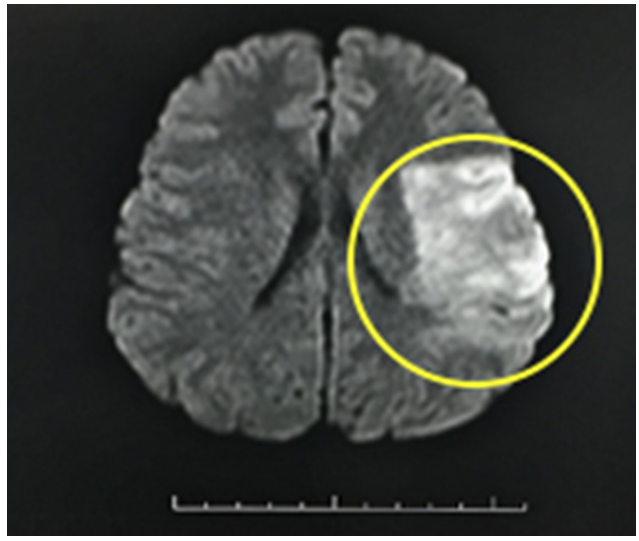

Figure 6. Frontotemporoparietal Infarct marked by circle.

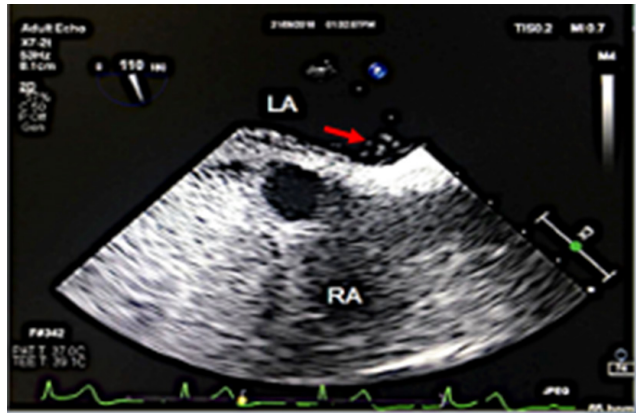

Figure 7. Bubbles (red arrow) are crossing from PFO.

heart functions, normal cardiac chamber size, normal regional wall motion, and no LV thrombus. TEE presented a small calcified atheroma plaque at the aortic arch and a positive bubble contrast study (Figure 4). Seven days holter monitoring recorded occult paroxysmal atrial fibrillation (Figure 5). She received statins, antihypertensive drugs, and anticoagulants.

Case 3

A 14-year-old boy presented with sudden weakness in his right upper and lower limbs, and difficulty speaking. Physical examination showed a decrease of motor strength in the right limbs and aphasia. ECG was normal, and his labs revealed an elevated d-dimer

level (0.96). NC-MRA of the head was obtained, which demonstrated an acute infarction in the left frontotemporoparietal and stenosis in the M3 segment of the left cerebral artery (Figure 6). TTE showed a small shunt in the atrium, suspicious of PFO. TEE with bubble contrast study presented a PFO type 1 with a left to right shunt (Figure 7). Further hypercoagulability testing showed that this child had a problem with protein C and S deficiency. The patient currently is not referred for percutaneous closure.

Discussion

CS has several definitions. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) defines CS as a cerebral infarct not attributed to a definite source of cardioembolism, large-vessel atherosclerosis, or small-vessel disease, despite (1) extensive cardiac, vascular, hematologic, and serological evaluation; (2) evidence of more than one competing cause, or (3) incomplete diagnostic evaluation. Meanwhile, according to the Causative Classification of Stroke System (CCS), diagnostic of CS requires a minimum evaluation of 12-lead electrocardiogram, echocardiogram, and brain imaging (computed tomography (CT) / magnetic resonance imaging (MRI), and intravascular imaging. The CCS divides CS into two categories: cryptogenic embolism and other cryptogenic origin. Determination of the culprit is essential to improve secondary stroke prevention strategies.[5] In summary, CS is a diagnosis of exclusion — it is an ischemic stroke with no identifiable etiology.

The role of PFO as a culprit, a risk factor, or coincidental finding is still debatable. The association between PFO as a culprit is a controversial issue, paradoxical embolism (the systemic passage of thrombi of venous origin through an interatrial conduit) frequently remains a diagnosis of suspicion. The incidence of PFO as a risk factor was found to be four times greater in patients under 55 years than in older patients.[4] There are several factors to consider when attributing a PFO to be stroke-related rather than incidental. Kent et al. developed an index to identify stroke-related vs. incidental PFO in CS. The study showed that decreasing age, the absence of conventional vascular risk factors, and the presence of a superficially located lesion are consistently associated with an increasing prevalence of PFO in patients with CS.[6] Furthermore, PFO morphologies that carry a higher risk of cerebrovascular accident include greater PFO height during a Valsalva maneuver, larger septal excursion distance, concomitant atrial septal aneurysm, and a large right-to-left shunt.[7]

Several potential CS mechanisms due to PFO are paradoxical embolism, insitu clot formation, and arrhythmias. In studies as early as 1877, an autopsy of a young stroke patient had shown significant lower limb thrombus along with a large PFO. He hypothesized that the PFO served as a pathway for an arterial embolism that paradoxically started in the venous circulation. Secondly, insitu clot formation is possible due to the deceleration of flow, blood stagnation and thrombi formation within the PFO or atrial septal aneurysm. Thirdly, embolic events in PFO are caused by atrial tachyarrhythmias and/or paroxysmal atrial fibrillation (AF), especially in the presence of a hypermobile atrial septum.[4] Occult paroxysmal AF is often asymptomatic and not identified by standard short term cardiac monitoring.[3] In a meta-analysis study, ECG at admission showed undiagnosed AF in 7.7% of cases. The length of monitoring to detect occult AF is still discussed. The current pathophysiology states that the relationship between AF and stroke starts from altered electrical activity in the atrial cells itself. This problem stimulates platelets, coagulation cascade, and thrombus formation, which are linked to stroke.[8]

The main target for therapy in CS is prevention of stroke recurrence and disability. Modalities of treatment include antiplatelet/anticoagulant and/or PFO closure.[9] The relationship between CS and PFO is mainly found in people under the age of 55 years. It is considered that after the first CS, there will be a risk of recurrent stroke by an average of 2% each year. The Risk of Paradoxical Embolism (RoPE) score is a scoring tool to predict the probability of CS associated with PFO and is used to estimate the risk of 2-year recurrence of stroke / TIA. Variables of the RoPE score include age, information on imaging, smoking history, stroke or transient ischemic attack history, diabetes history, and hypertension. The higher score indicates the stroke is more PFO related. PFO is considered to be closed if the score above or equal to 7.[10]

In case 1, the patient had repeated strokes even with optimal medical therapy. The RoPE score was 7. This means that the probability of CS associated with PFO is high. In this case, PFO is considered pathogenic

rather than an incidental finding. PFO closure is the best choice for preventing the recurrence of paradoxical embolism through PFO.

In Case 2, the patient had a history of hypertension and dyslipidemia, well known risk factor for stroke. However, as the patient had experienced recurrent strokes, further TEE and holter evaluation was done. MRI revealed multiple infarct sites in the cortical area and lesions within multiple vascular regions. It is assumed that the stroke is cardioembolic, with PFO and occult AF as a risk factor of CS. Both PFO and atrial fibrillation is a condition linked to ischemic stroke. Daher et al, reported PFO prevalence of 18.7% using TEE and 56.6% during the pulmonary vein isolation ablation procedure in AF patients.[11] As a structured congenital heart disease, PFO is also linked to AF. Atrial arrhythmias increase with increasing age to up to 38% in 50-year-old patients. This also comes with a 13% risk of TIAs and stroke.[12]

Our patient had both PFO and atrial fibrillation. Anticoagulation was used and no PFO closure had been done. The presence of concurrent PFO in this largely anticoagulated group of patients with AF was not associated with increased risk of ischaemic stroke. The presence of PFO in patients with AF was not associated with embolic risk beyond those with right-to-left shunt and other established risk factors in this predominantly anticoagulated AF population.[13]

In case 3, CS was presented at a young age. The patient presented with PFO and protein C/S deficiency. Thrombophilia is a known risk factor of thrombus formation. This hypercoagulable state is believed to be the primary cause in the creation of the paradoxical emboli in this patient. However, it is noted that the presence of thrombophilia typically predisposes a patient more frequently to venous rather than arterial thrombosis. There are several potential mechanisms that could contribute to the development of ischemic stroke. Ischemic stroke may arise in the setting of deep vein thrombosis and subsequent paradoxical embolism via a PFO. Therefore, CS patients with patent foramen ovale should also be investigated for deep venous thrombosis in the legs and pelvic veins.[1415]

Ischemic stroke resulting from thrombophilic disorders may involve any arterial territory and often affects multiple arterial territories at the same time. In this case, the patient experienced CS manifesting as left temporal region infarction along with stenosis in the middle cerebral artery, as seen on the imaging study.[14]

The presence of a PFO is associated with an increased risk of CS, especially in the young. However, there is only limited evidence with regards to the impact of thrombophilia and the risk of recurrent CS with PFO. A systematic review by Hviid et al suggests that the presence of an acquired or inherited thrombophilia in patients with CS and PFO increases the risk of recurrence, even after PFO closure. PFO closure may reduce the risk of stroke recurrence but additional antithrombotic therapy is still needed to give a maximum protection to its recurrence.[14, 16] Therefore, in this case PFO closure may be considered however, it may not be entirely necessary.

Conclusion

This paper presented 3 different cases of CS with PFO. Determining PFO as a CS cause remains a challenging task. Clinical presentation, morphology of PFO and RoPE score could be used to determine PFO pathogenicity and risk of stroke recurrence. The management goal of patients with PFO and CS include the prevention of stroke recurrence and disability.

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Conflicts of interest

None.

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