13 Paradoxical Embolic Stroke

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Abstract

Even after extensive work-up for stroke etiology, up to 40% of ischemic stroke patients do not have identifiable cause, who are considered cryptogenic stroke. Paroxysmal embolism refers to embolism originated from venous circulation entering arterial circulation, potential cause of the cryptogenic stroke. To the development of ischemic stroke with paradoxical embolism, there are essential components including embolic source in venous system, intracardiac or intrapulmonary communication with right-to-left shunt, and embolization to cerebral circulation. There are multiple image modalities including echocardiography, transcranial Doppler, MR and CT images which can provide diagnostic and functional information of the right-to-left shunt. Most common structure of right-to-left shunt is patent foramen ovale (PFO). Epidemiological data consistently have reported that higher prevalence of PFO in patients with cryptogenic stroke than controls. Recently, randomized clinical trials demonstrate benefit of endovascular closure of PFO in cryptogenic stroke patients with PFO than only medication for secondary prevention of stroke. However, there is a need for caution to interpret the results because it is difficult problem to determine whether the presence of PFO is the cause of paradoxical embolism or only incidental finding. Paradoxically, recurrent risk of stroke is lower in patients with a high probability of a PFO-related stroke than those with other etiology. There is a need for further studies to identify patients at high risk of paradoxical embolism and optimal treatment plan.

13.1 Paradoxical Embolism

Ischemic stroke is a pathophysiological heterogenous disease. Despite extensive stroke workup, there are up to 40% of patients whose underlying cause remained unexplained, commonly referred to cryptogenic stroke [1]. Cryptogenic stroke frequently demonstrates the pattern of embolic stroke without compelling source. Paroxysmal embolism refers to thromboembolism originated from the venous side of circulation to the arterial side through an intracardiac or extracardiac shunt. Essential components to develop paradoxical embolism are venous thrombosis (source of embolism), right-to-left shunt, and embolism into arterial circulation (Fig. 13.1). Increasing evidences suggest that paroxysmal embolism is one of the major hidden causes of cryptogenic stroke,

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S.-H. Lee (ed.), *Stroke Revisited: Pathophysiology of Stroke*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1430-7_13

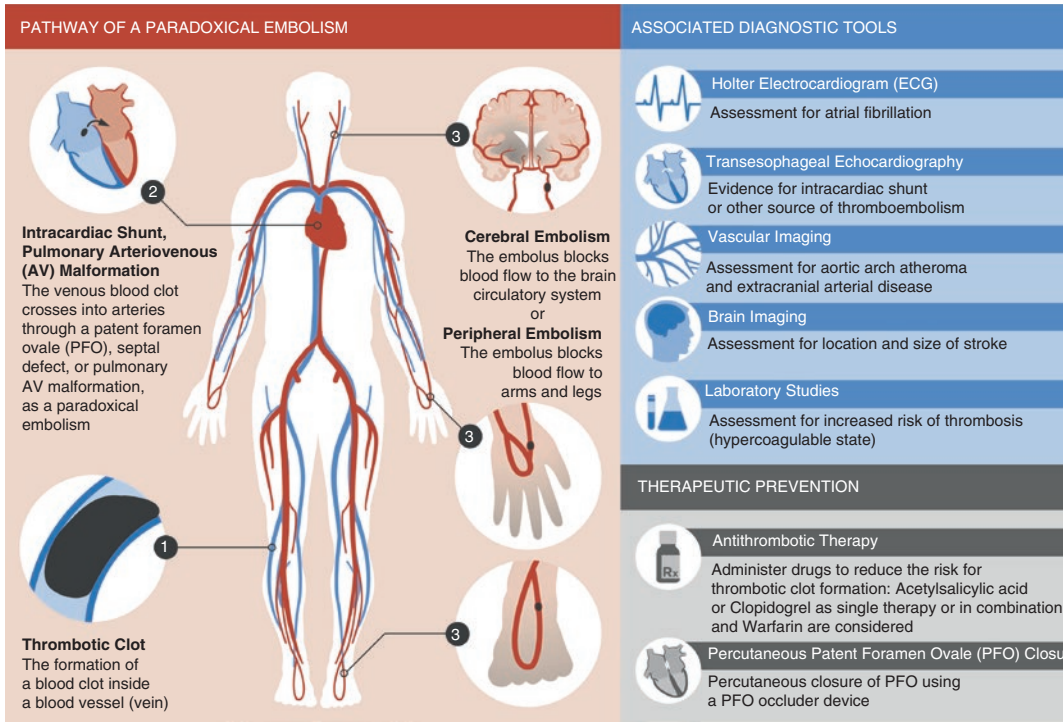

Fig. 13.1 Paradoxical embolism. Figure is from reference [1]

and the shunt structures may be potential treatment target to prevent recurrent stroke. In this chapter, we discuss the mechanism, intracranial/extracranial shunt, diagnostic method, and proper management for the prevention of paradoxical embolism based on currently available data.

13.2 Source of Embolus

Paradoxical embolism starts with the formation of blot clot in the venous circulation. Venous thrombosis, blot clot in vein, is relatively common medical problem with an annual incidence that exceeds 1 per 1000. Risk of venous thrombosis varies by race, with African-Americans having over fivefold greater incidence than Asian-ancestry populations, and an intermediate risk for European and Hispanic populations [2]. Along with the genetic susceptibility, recent surgery, trauma, immobilization, obesity, oral contraceptives, and coagulopathy are well-known predisposing factor for venous thrombosis. A large portion of venous thrombosis is asymptomatic, but both symptomatic and asymptomatic cases can be a source of pulmonary or paradoxical embolism. In patients with venous thrombosis, asymptomatic pulmonary embolism is also frequently found. Most common site of venous thrombosis is the deep vein of legs (deep vein thrombosis, DVT) [3]. In study of pulmonary embolism, about 90% of embolism seems to be originated from leg vein [4]. Superficial vein as well as deep vein can be the source of embolism.

Duplex ultrasound on leg vein is most commonly performed diagnostic study to find source of venous thrombi. However, failure to find the evidence of venous thrombi with ultrasound study is common in patients presumed due to paradoxical or pulmonary embolism. There are many possibilities of resolution of venous thrombus with anticoagulation, complete migration of thrombus, and thrombus in calf, upper extremities or pelvic vein which are usually unevaluated [3]. One recent study reported that 18% of

cryptogenic stroke patients who underwent pelvic MR venography had pelvic venous thrombosis [5]. For patients who highly suspected to paradoxical embolism, whole leg ultrasound, CT venography, MR venography and conventional contrast venography could be used as diagnostic tools with high diagnostic accuracy. Thrombosis in upper extremities is relatively rare but accounts for 4–10% of venous thrombosis [6]. Many cases in upper extremity are intravenous catheter-related thrombosis.

D-dimer is the degradation product of cross-linked fibrin and D-dimer level in blood correlate with the presence of fibrin clots. Because D-dimer level is elevated in cases with venous thrombosis, D-dimer test is frequently performed in clinical practice. However, D-dimer test has high sensitivity and poor specificity for venous thrombosis. In patients with clinically suspected venous thrombosis, low level of D-dimer should not be interpreted to obviate the possibility of venous thrombosis.

13.3 Right-to-Left Shunt

Without structure of right-to-left shunt, emboli originated from venous thrombosis travels into pulmonary circulation causing pulmonary embolism, which do not enter to arterial circulation. Cryptogenic stroke with paroxysmal embolism should accompany with the right-to-left shunt via intracardiac (patent foramen ovale, congenital heart defects) or extracardiac route (pulmonary arteriovenous malformation). In the cases of intracardiac shunt, the mean right atrial pressure is usually lower than the mean left atrial pressure which prevents right-to-left shunt flow and embolization. However, physiologic spontaneous transient reversal of the atrial pressure is present during early diastole and during isovolumetric contraction of the right ventricle of each cardiac cycle [3]. The reversed gradient can further increase with physiologic maneuver or conditions which increase pressure of right atrium or pulmonary vascular resistance such as postural change, inspiration, coughing, Valsalva maneuver, obstructive sleep apnea, chronic obstructive pulmonary disease, pulmonary embolism, right ventricular infarction, and positive end-expiratory pressure. These factors enhancing right-to-left flow can promote emboli travel into arterial circulation, which increases the risk of paradoxical embolism in the cases with structure of right-to-left shunt.

13.3.1 Patent Foramen Ovale

PFO is a hole between the left and right atrium, the most common congenital defects can act as intracardiac shunt. During fetal circulation, the hole works as physiologic route for oxygenated blood from the placenta to the systemic circulation. Spontaneous closure occurs at infancy, but the hole remains open in about 20–30% of general population; this condition is called PFO. There is no sex predominance and the size of PFO ranges from 1 to 19 mm in autopsy studies. Although it is not well known whether the size of PFO changes over time, the size of detected PFO is larger in older than young individuals in the cross-sectional studies. This finding might be due to spontaneous closing with aging in cases with small size of PFO, remaining only unclosed large size of PFO in elderly patients.

It has been widely debated whether PFO is a risk factor of ischemic stroke and paradoxical embolism for a long time. There were case reports of autopsy with systemic embolization and branched thrombus entrapped within PFO. In the cross-sectional studies, the prevalence of PFO is consistently higher in ischemic stroke patients than controls. PFO is more common in cryptogenic stroke than stroke with other causes, especially in young patients [7]. As another supporting evidence for the pathophysiological role of PFO on paradoxical embolism, PFO is a significant risk factor of death and arterial thromboembolic complications in patients with pulmonary embolism [8]. The presence of PFO is also a risk factor of stroke or transient ischemic attack in those who underwent implantation of transvenous pacemaker or defibrillator which may be the

Characteristics	Points
No history of hypertension	1
No history of diabetes	1
No history of stroke or TIA	1
Nonsmoker	1
Cortical infarct on imaging	1
Age(year)	
18–29	5
30–39	4
40–49	3
50–59	2
60–69	1
≥ 70	0
Maximum score	10

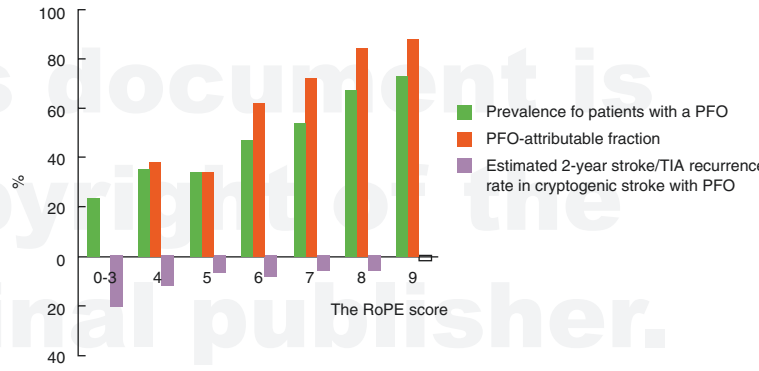

Fig. 13.2 Paradoxical embolism (RoPE) score. *TIA* transient ischemic attack. Figure is from references [14, 15]

source of venous thrombosis [9]. On the other hand, coexisting or preceding event of venous thrombosis is frequent in patients with suspected PFO-related strokes [10].

Considering the pathologic evidence of trapped thrombus in autopsy cases, PFO could be anatomical route of paradoxical embolism into cerebral circulation and risk factor of cryptogenic stroke. Epidemiologic data also support the relationship between PFO and cryptogenic stroke. However, because PFO is prevalent in general population (20–30%), it is difficult to determine whether PFO is the cause of stroke or only incidental finding when PFO is found in stroke patients. Clinical manifestations of PFO-related stroke are nonspecific, and there is no conclusive diagnostic test for paradoxical embolism. Based on Bayers' theorem and prior reports for the prevalence of PFO, probably one-third of PFO found in patients with cryptogenic stroke is likely to be incidental [7]. To estimate whether PFO is a cause of stroke and risk for recurrent stroke in patients with PFO, clinician should consider multiple anatomical and functional factors. There are many anatomical variants that may be linked with stroke risk in the patients with PFO; large size of PFO, long tunnel length (maximum overlap of the septum primum and septum secundum), aortic septal aneurysm, prominent Chiari network and Eustachian value [11]. These structures are considered to enhance direct flow toward PFO or increase in pressure of right atrium, which may predispose to paradoxical embolism in the cases with PFO. Higher degree of right-to-left shunt is more frequently found in patients with cryptogenic stroke than those with other causes [12]. Right-to-left shunt at rest without Valsalva maneuver (severe degree) and bidirectional flow through PFO are considered high risk of paradoxical embolism [13]. High degree of shunt is one component of RoPE score which estimates the likelihood of the PFO-related stroke (Fig. 13.2) [14]. However, prior studies are mainly based on cross-sectional design and inconsistent findings are also present. Underlying role of the anatomical and functional features with PFO on cryptogenic stroke is not fully elucidated. We need further data whether these findings are reliable risk markers for paradoxical embolism in PFO patients.

13.3.2 Atrial Septal Defect and Other Intracardiac Shunt

Along with PFO, there are other intracardiac communications which can be a route of paradoxical embolization including atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus, and Ebstein's anomaly. ASD, a hole in the wall between right and left atrium, allows intracardiac shunt for right-to-left flow and lowering of oxygen levels in arterial circulation. ASD is the third most common type of congenital heart defect with a dominance of female and an incidence of 56 per 100,000 live-

births [16]. The symptom and nature of ASD depend on the type, size, and coexisting factors. VSD is a defect in the ventricular septum and one of the most commonly encountered congenital heart defects at birth. About 2–5% of babies have VSD at birth, and small defects often are asymptomatic and close spontaneously during childhood [17]. Large VSD can increase pulmonary resistance and workload on heart and lung leading to multiple cardiopulmonary complications. Usually, VSD is associated with left-to-right shunt, but right-to-left shunt flow through ventricular shunt is possible and could be related to paradoxical embolism. In VSD patients, coexisting cardiac abnormalities (Eisenmenger syndrome and tetralogy of Fallot) are frequent, which can predispose to right-to-left flow.

13.3.3 Pulmonary Arteriovenous Malformation, Extracardiac Shunt

Pulmonary arteriovenous malformation (PAVM) is abnormal vascular communication between pulmonary artery and pulmonary vein which allows persistent right-to-left shut and passenger of venous thrombus into arterial circulation. One of the major functions of pulmonary capillary bed is filtering of small thrombi and bacteria from venous circulation. Defect in filtration and direct shunt by PAVM can increase the risk of paroxysmal embolism and brain abscess. PAVM is commonly asymptomatic, but can cause hypoxemia, cyanosis, exercise intolerance, hemoptysis, brain abscess, and stroke. There may be contributing factors of coexisting polycythemia or cerebral arteriovenous malformation with PAVM. PAVM could be acquired with severe liver disease or chronic infection. There is only limited data for stroke risk with PAVM. In studies with patients with PAVMs, the prevalence of stroke or TIA varied from 2.6% to 37.0% [18, 19].

Unlike intracardiac shunt structures, venous flow can enter arterial side though PAVM even without reversal of the pressure gradient to right-left. PAVM is a relatively rare vascular disease, occurring at a frequency of 0.02% [20]. The male-to-female ratio varies from 1:1.5 to 1.8. Approximately 50–70% of PAVMs are present in the lower lobes. PAVM can be single or multiple, unilateral or bilateral. Single PAVMs range from 42% to 74%, and bilateral PAVMs range from 8% to 20% [21, 22]. PAVM can be classified as simple or complex types on the basis of their vascular architecture. Simple type has a single segmental feeding artery and complex type has multiple segmental feeding arteries. It is not well known whether characteristics of PAVM including the presence of respiratory symptoms, feeding artery size, degree of the right-to-left shunt are associated with stroke risk [23].

Sporadic or acquired PAVMs are possible, but >80% of PAVM occur in patients with an inherited condition called hereditary hemorrhagic telangiectasia (HHT), an autosomal dominant disorder. For the patients with confirmed or suspected HTT, screening for brain and PAVM is recommended [18]. In HTT patients, the prevalence of PAVMs has been estimated between 15% and 33%. In one clinical report of patients with PAVM and HTT, most patients were asymptomatic until stroke and did not previously diagnose for PAVM [23]. In Asians, PAVM may be less associated with HHT than Western populations [24].

Not all patients with PAVM need treatment. Most PAVMs remain stable in size, with approximately 25% enlarging slowly. Growing of PAVM occurs most during pregnancy or puberty which supports the influence of hormone. Common indications for treatment of PAWM are progressive growth, feeding artery size >3 mm, symptomatic hypoxemia, paroxysmal embolism, or brain abscess.

13.4 Diagnosis

Because stroke is a heterogenous disease, it is a difficult problem to determine whether right-to-left shunt is a cause of stroke by paradoxical embolism or incidental finding in the stroke patients with right-to-left shunt. To evaluate the likelihood for paroxysmal embolism, we should

comprehensively consider the pattern of ischemic stroke in the brain, conventional risk factors, and the presence and characteristics of right-to-left shunt.

13.4.1 Brain Image

At brain image, paroxysmal embolism is expected to have similar infarction pattern of embolic stroke. Embolic stroke commonly shows multiple infarct lesions in different vascular territories with scattered or cortical-subcortical involvements. Presence of silent brain infarction in different vascular territory also suggests the presence of embolic cause. In angiographic study, occlusion of cerebral artery at acute phase and resolution of the occlusion later strongly indicate embolic stroke. If patients with image pattern of embolic infarction do not have other sources of embolism, clinician should concern the possibility of paroxysmal embolism especially in young patients. Even in cryptogenic stroke, brain infarct pattern may vary according to the shunt characteristics and coexisting anatomical variants [15]. Cortical involvement is one component suggesting stroke attributable to the PFO [14]. However, stroke with paradoxical embolism can present with patterns of small vessel disease or other causes of stroke. Currently, there is no standardized image criteria and it should be improper to diagnose paradoxical embolism only by findings of brain image at stroke.

13.4.2 Study for Shunt

Detection of intracardiac or extracardiac shunt is important to both diagnosis and treatment plan for cryptogenic stroke. As diagnostic test for shunts, commonly available tools are transcranial Doppler (TCD), echocardiography, cardiac CT, and MR images. Echocardiography is the most popular study for the investigation of cardiac source of stroke. It can provide information on intracardiac shunt and other embolic cause in heart (myxoma, intracardiac thrombus, valvular disease). For more accurate detection of shunt with echocardiography, peripheral injection with agitated saline or echocardiac contrast is required with Valsalva maneuver. For detection of right-to-left shunt including PFO, transthoracic echocardiography (TTE) can be easily performed non-invisibly with relatively good sensitivity and specificity [3]. However, TTE is inappropriate for detection of small shunt, and transesophageal echocardiography (TEE) is more recommended for detection of PFO. TEE also has merits over TTE with clearer images on aorta, atrium, atrial appendage, and atrial septum that are important structures on cardioembolic source. On the other hand, TEE needs fasting and cooperation of the patient during procedure, which was frequently unsuccessful in acute stroke patients. On the TEE examination with intracardiac shunt-like PFO, microbubble signal enters left atrium within three cardiac cycles after appearance of microbubble in right atrium. In extracardiac shunt-like PAVM, bubbles enter left atrium after 3–8 cardiac cycles.

Along with echocardiography, TCD can be used to evaluate the presence and degree of intracardiac and extracardiac shunt. With peripheral injection of agitated saline and Valsalva maneuver, microbubble signals in middle cerebral artery can confirm the presence of shunt structures. The degree of the shunt on TCD examination could be quantified based on the number of microbubble signals as 0 = absent shunt (Grade 0); 1–20 = small shunt (Grade 1); >20 with no curtain = moderate shunt (Grade 2); >20 with curtain effect = large shunt (Grade 3) [25]. In cases with poor temporal window for TCD study, microbubble signals also can be accessed in extracranial or peripheral limb artery. Compared to TEE, TCD study has merits of good sensitivity, simplicity, noninvasiveness, and high feasibility [26].

Recently, the use of CT and MRI has increased for diagnosing intracardiac and extracranial shunt due to feasibility and no need for Valsalva maneuver. Electrocardiographically gated multidetector CT can detect intracardiac shunt with relatively good accuracy and provide detailed images of cardiac structures. The diagnostic accuracy of magnetic resonance image for cardiac shunt remained controversial, but maybe useful for noninvasive quantification of

shunt flow. PAVM can be diagnosed with radionuclide perfusion lung scanning, CT, MRI, and pulmonary angiography. On plain chest X-ray, PAVM is frequently apparent as oval mass lesion with uniform density. Contrast enhanced computed tomography is the diagnostic imaging modality of choice for PAVM with higher detection rate for PAVM rather than conventional pulmonary angiography (98% vs 60%) [27]. Pulmonary angiography remained as gold standard for the evaluation of PAVM for not only identification but also angioarchitecture of pulmonary vasculature. There is screening technique using ear oximetry for detection of cardiac shunt. If there is enough shunt flow during Valsalva maneuver, mixed desaturated venous flow causes drop of oxygen saturation in arterial side. Compared to the result of TEE, the sensitivity and specificity of ear oximetry are 0.756, 0.706 in one preliminary study [28].

13.5 Treatment and Prevention for Paradoxical Embolism

For patients who have intracranial or extracranial shunt and suspected with paradoxical embolization by the shunt, the treatment and preventive strategy should be individualized based on underlying shunt structure and risk of recurrence. Main clinical concerns are (1) whether shunt structure is the cause of stroke or incidental finding; (2) obliteration of the shunt may be preventive for recurrent stroke; and (3) optimal medication plan.

13.5.1 Patent Foramen Ovale

Although PFO could be a route for paradoxical embolism, there is long-term debate in whether PFO is a significant risk factor for ischemic stroke. Cross-sectional studies consistently show high prevalence of PFO in stroke patients compared to controls. However, many population-based cohort studies do not find increased risk for ischemic stroke in those with PFO [29]. These findings suggest that fraction of primary stroke risk attributable to the PFO may be low in the general population, especially in the elderly. Therefore, primary stroke preventive treatment for PFO is not indicated to the healthy people without prior embolic events in the absence of other significant complications. Major controversy in the clinical practice is preventive plan for patients with ischemic stroke who have PFO. To set optimal preventive plan, we should access the underlying etiology of the primary stroke. Because PFO is common in the general population, PFO in stroke patients could be both cause of paradoxical embolism or incidental finding not related to stroke. Risk of Paradoxical Embolism score (RoPE) is a 10-point clinical scoring system to predict the likelihood of PFO in patients with cryptogenic stroke based on 12 component databases (Fig. 13.2) [14]. The RoPE score is calculated with the evidence of cortical stroke on neuroimaging, the absence of conventional risk factors (hypertension, diabetes mellitus, smoking, previous TIA, or stroke) and young age; these factors are related with the likelihood of paradoxical embolism. In the stroke patients with PFO, high RoPE score suggests that the discovered PFO is likely to be cause of stroke than incidental finding. Paradoxically, stroke recurrent rates decrease as the RoPE score increases [14, 30]. Indeed, many observational studies failed to find increased risk for recurrent stroke with the presence of PFO. These paradoxical features could be explained that the recurrent risk in patients with PFO-related stroke may be lower than those with other conventional stroke mechanisms.

If the underlying cause of primary stroke is suspected to paradoxical embolism through PFO, closing of the shunt may be the fundamental prevention of recurrent embolism. PFO, a hole between atrial septum, can be closed with heart surgery or endovascular devices. Recently, there are randomized control trials based on the hypothesis that PFO closure using endovascular devices may have stroke-preventive effects. Table 13.1 summarizes results of the randomized trials. In the earlier studies of CLOSER I, PC, and RESPECT trials, PFO closure group had lower risk for recurrent throm-

Table 13.1 Trials of patent foramen ovale closure for stroke prevention

Trial name (year of publication)	No. of patients	Mean or median no. of years of follow-up	Comparator	Primary outcome	Hazard ratio[a]	*P* value[a]
Trials with negative findings						
CLOSURE I (2012)	909	2	Antiplatelet therapy, warfarin, or both	Composite of stroke or transient ischemic attack at 2 years, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years after randomization	0.78	0.37
PC (2013)	414	4.1 (PFO closure group), 4.0 (medical-therapy group)	Antiplatelet therapy or anticoagulation[b]	Composite of death, stroke, transient ischemic attack, or peripheral embolism	0.63	0.34
Trials with positive findings						
Gore REDUCE (2017)	664	3.2	Antiplatelet therapy	Ischemic stroke and new brain infarction on imaging	0.23	0.002
CLOSE (2017)	473	5.3	Antiplatelet therapy or anticoagulation[b]	Stroke	0.03	<0.001
RESPECT extended follow-up (2017)	980	5.9	Antiplatelet therapy or warfarin	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization	0.55	0.046

CLOSE denotes Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence, CLOSURE I Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale, Gore REDUCE Gore HELEX Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale (PFO), PC Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism, and RESPECT Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment. Table is modified from *Stroke and Vascular Neurology* 2018; 3;e000173 [31]

[a]The hazard ratio and *P* value are for the expected probability of stroke or other primary outcome after closure of the PFO versus medical treatment in the intention-to-treat analysis

[b]Anticoagulation refers to any form of anticoagulation

boembolism than medical treatment group, but the difference did not reach statistical significance. On the other hand, two more recent trials of Gore REDUCE and CLOSE succeeded in demonstrating that PFO closure is preventive for stroke recurrence compared to only medical treatment. The Gore REDUCE trial demonstrated 77% relative reduction of recurrent strokes with PFO closure compared to medication group; the number needed to treat of PFO closure to prevent one new stroke is 28 at 2 years. The CLOSE trial showed 4.9% absolute risk reduction of recurrent stroke for 5 years with PFO closure; the number needed to treat with PFO closure to avoid one stroke at 5 years is 20. The discrepant results between the early and later trials might be due to the more stringent criteria to include only patients whose PFO was suspected to be a cause of primary stroke [32]. CLOSE trial only includes patients with large shunt (>30 microbubbles) or an atrial septal aneurysm which are supporting findings of PFO-related stroke. Gore REDUCE trial excluded patients who had suggesting features of any other cause including atherosclerosis on cerebral artery or aortic plaque,

cardioembolic source, and image pattern of small-vessel occlusive disease. In the later trials with more strict inclusion criteria, recurrent stroke risk was significantly lower in those who received endovascular PFO closure than controls who received only medication. Furthermore, subgroups with large shunt or coexisting atrial septal aneurysm, suggesting PFO-related stroke, have more benefit with PFO closure. Stroke preventive effect of PFO closure is also found in the RESPECT extended follow-up study [33]. In the above five trials, success rate of PFO-closing rates ranged from 89.4% to 99.6%. Procedure-related complications and adverse events are relatively infrequent with vascular injury, device-related embolization, incomplete closure, and residual shunt on PFO. One concern with PFO-closing device is increased risk of newly developed atrial fibrillation [34].

Until 2017, major guidelines of stroke do not recommend PFO closure as preventive treatment for stroke patients with PFO. The guidelines are published prior to the recent randomized trials and did not reflect the results. Considering the positive results in the multiple trials, PFO closure could be beneficial to prevent recurrent stroke to selected patients who are suspected to PFO-related stroke. However, clinician should not routinely decide PFO-closing to all stroke patients who have not identifiable causes; about 40% of all stroke patients are undetermined etiology. The PFO trials showing beneficial findings selectively included patients <60 years who are more likely to have stroke-related PFOs. If patients are of old age or have multiple conventional risk factors, which suggest atherosclerotic or other stroke mechanism rather than PFO, it is hard to expect the preventive effect of PFO closure. Currently, there is a lack of specified consensus or guidelines who is the candidates of PFO-closing in stroke patients. For planning of PFO closure should be decided based on individual's characteristics including radiological and functional studies for PFO and coexisting conventional risk factors (Table 13.2). Although reported complication rate is low with endovascular PFO closure, critical adverse event is possible.

Table 13.2 Features suggesting a causative relationship between PFO and paradoxical embolism in stroke

History
Sedentary period prior to onset
Valsalva at onset
Absence of common stroke risk factors
Anatomy
Atrial septal aneurysm
Large PFO size
Prominent Eustachian valve
Physiology
Shunt at rest
Spontaneous Doppler flow
Many bubbles cross on contrast injection
Neuroimaging and laboratory testing
Past "silent" strokes
Embolic stroke topography
Hypercoagulable state

PFO patent foramen ovale
Table is from *Curr Atheroscler Rep* 2007; 9;319–325 [35]

13.5.2 Arterial Septal Defect and Ventricular Septal Defect

ASD can introduce complications of paradoxical embolization, cerebral abscess, arrhythmia, right ventricular heart failure, and pulmonary hypertension. Generally, ASD closure is indicated to the patients with right ventricular overload [36]. Surgical repair of VSD is indicated for significant aortic regurgitation, pulmonary hypertension, and refractory heart failure. Due to the limited data, there is lack of direct evidence whether ASD or VSD closure can reduce risk of stroke recurrence. Unlike PFO, ASD and VSD are relatively uncommon in adulthood. If the intracardiac communications are found at work-up for ischemic stroke and there is no other compelling cause of stroke, clinicians should consider the possibility of paradoxical embolism and the need of therapeutic closing of the heart defects. Considering the mechanism of paradoxical embolism and prior positive data from trials with PFO closure, closure of ASD or VSD might be reasonable to prevent further cryptogenic stroke in the absence of other cause of embolism.

13.5.3 Pulmonary Arteriovenous Malformation

The prevalence of PAVM is reported very low in general population. Therefore, if PAVM is detected in stroke patients with pattern of embolic stroke and without other plausible causes, treatment of PAVM should be considered for prevention. Treatment of PAVM could be done by endovascular embolization or microsurgery. Success rate of endovascular embolization is as high as 98%, and neurological complication rate is low after successful embolization [22].

13.5.4 Antiplatelet or Anticoagulation for Paradoxical Embolization

Optimal medication plan is another debate for PFO-related stroke. For the prevention of venous thromboembolism, anticoagulation is considered to be more effective than antiplatelet [37]. Because paradoxical emboli are originated from venous thromboembolism, anticoagulation may be more preventive to the patients who presented with cryptogenic stroke through supposed paradoxical embolism. Indeed, some study data suggested anticoagulation might be more reasonable than antiplatelet for secondary prevention in cases with PFO [38]. However, anticoagulation with vitamin K antagonist is consistently associated with higher bleeding risk than antiplatelet. Therefore, current guidelines do not support routine use of anticoagulant for patients with PFO or cryptogenic stroke except in coexistence of deep vein thrombosis. The prior trials of endovascular PFO closure had control groups treated with antiplatelet. There is a lack of conclusive data comparing the preventive effects of PFO closure and anticoagulation. New oral anticoagulants (NOAC) are alternative anticoagulants which are at least as effective as vitamin K antagonist for prevention of thromboembolism in patients with atrial fibrillation and have lower risk of bleeding than vitamin K antagonist. Ongoing trials for NOAC on embolic stroke of undetermined source might provide further information for the optimal medication strategy for paradoxical embolism.

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