Contemporary Approach to Paradoxical Embolism
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Case Presentation
A 63-year-old man with a history of systemic hypertension presented to the emergency department for evaluation of acute chest pain and shortness of breath that occurred while he was shoveling heavy snow. His heart rate was 114 bpm and blood pressure was 142/78 mmHg. Peripheral oxygen saturation was 91%, and his respiratory rate was 20 breaths per minute. During the physical examination, he developed severe left arm pain associated with complete loss of the left radial and brachial pulses. Urgent upper-extremity angiography demonstrated acute thromboembolism of the proximal left axillary artery (Figure 1A). Percutaneous transluminal embolectomy, followed by catheter-directed thrombolysis, was performed to successfully treat the arterial thrombus. However, thoracic computed tomographic angiography demonstrated complete occlusion of the left subclavian artery and thrombus within the left brachial artery. To evaluate this further, transesophageal echocardiography with agitated saline contrast was performed and demonstrated a patent foramen ovale (PFO) with evidence of right-to-left intracardiac shunt (Figure 1C). Three recent studies provide, for the first time, data from prospective, randomized trials to guide treatment in patients with PFO and paradoxical embolism.1–3

Overview
Interatrial shunt through the foramen ovale, an oval-shaped window within the septum secundum, is an essential component of fetal circulation that permits the communication of blood oxygenated in the placenta with deoxygenated blood in the left atrium. At birth, right atrial pressure and pulmonary vascular resistance rapidly drop and left atrial pressure rises, forcing the flexible septum primum against the muscular septum secundum, leading to physiological closure of the foramen ovale in a process that typically occurs by 2 years of age.4 Septum primum--foramen ovale coaptation failure, however, results in a PFO. According to autopsy registries, this occurs in ≈25% of the general population, although the mechanisms underpinning failure of the foramen ovale to close are incompletely understood.4

Contemporary Approach to PFO Diagnosis
The following noninvasive modalities are used to diagnose PFO in clinical practice.

Echocardiography
Transesophageal echocardiography (TEE) is the most effective study for detecting and describing PFO.5 Characterizing PFO shunt magnitude with TEE is a semiquantitative assessment performed by analyzing the Doppler profile or movement of agitated saline contrast across the interatrial septum. Limitations of TEE include procedural risks such as esophageal trauma, pain, and agitation, as well as sedation requirements. In fact, the sensitivity of TEE may be decreased by the inability to perform theValsalva maneuver properly as a consequence of sedation or an open glottis. Thus, transthoracic echocardiography may be used to screen for PFO. With the use of agitated saline contrast, transthoracic echocardiography achieves a sensitivity and specificity profile for detecting PFO akin to that of TEE.6
Transcranial Doppler

Transcranial Doppler leverages the detection of microbubbles in the cerebral circulation to diagnose PFO. In the presence of an intracardiac shunt (ie, PFO), agitated saline contrast injected into a peripheral vein traverses the interatrial septum and may be visualized by a characteristic Doppler signal pattern in the basal cerebral arteries. In a retrospective analysis of 222 patients undergoing both transcranial Doppler and TEE, 94% of intracardiac shunts identified by TEE were also detected by transcranial Doppler.7 Nevertheless, paradoxical emboli suspected by transcranial Doppler will often necessitate additional imaging to characterize shunt anatomy and identify potential cardiac sources of thromboembolism.

Cardiac Magnetic Resonance and CT Imaging

Cardiac magnetic resonance imaging is commonly used to measure the degree of left-to-right shunt in several congenital heart conditions. However, the sensitivity of detecting right-to-left shunt to diagnose PFO may be as low as 50% compared with TEE.8 Similarly, high-resolution cardiac CT, which uses superior spatial resolution to define cardiac structure and coronary anatomy, is limited for detecting PFO. In a series of 152 patients, cardiac CT demonstrated a sensitivity of only 73% for detecting PFO compared with TEE.9 The appropriateness of each noninvasive modality to diagnose PFO often depends on local expertise and patient contraindications. Overall, cardiac magnetic resonance imaging and cardiac CT remain relatively untested in clinical practice compared with TEE, and, thus, are generally regarded as secondary options for assessing PFO anatomy.

Clinical Significance of PFO

Numerous case-controlled and observational reports implicate PFO in the pathogenesis of cerebrovascular disease, particularly stroke and migraine headache.4,10 For example, among 416 patients evaluated at a tertiary referral center (2001–2009), indications

Figure 1. Clinical studies demonstrating paradoxical embolism. A 63-year-old man presented with chest pain and subsequently developed left arm ischemia from an axillary artery thromboembolism. Clinical investigation revealed the presence of a pulmonary embolism and patent foramen ovale, supporting a diagnosis of paradoxical embolism. A, Selective angiography demonstrates occlusive thrombus in the left axillary artery (arrowhead). B, Computed tomographic angiography of the pulmonary arteries identifies a filling defect within the right lower lobe pulmonary artery (arrowhead) extending into the segmental branches of the right lower lobes. Filling defects were also observed in the left lower lobe pulmonary artery and within the segmental branches of the left lower lobe. C, Transthoracic echocardiography performed ≈5 seconds after the injection of agitated saline contrast into a right antecubital intravenous line demonstrates the visualization of 18 microbubbles in the left atrium (LA) and left ventricle (LV), that is consistent with a moderate intracardiac shunt.
for PFO closure were idiopathic (ie, cryptogenic) stroke (n=219), transient ischemic attack (TIA; n=80), migraine headache (n=38), hypoxemia caused by an intracardiac shunt (n=14), and thromboembolism (n=12).11 Supporting the assertion that PFO is mechanistically involved in stroke are data indicating that ≈40% of ischemic strokes cannot be explained by atherosclerotic cerebrovascular disease, other traditional risk factors for stroke, or an obvious embolic source.1 Furthermore, the incidence of PFO is greater in patients with cryptogenic stroke compared with the nonstroke population, with some reports estimating that patients with cryptogenic stroke are 4-fold more likely to have a detectable PFO compared with normal control subjects.10 Although these and other studies demonstrate a clear association between PFO and cryptogenic stroke prevalence, causality is less certain when considering populations of patients. For example, in a recent report involving 1100 patients followed up for a mean of 11 years, the presence of a PFO did not substantially influence the risk of a first stroke.12 Nevertheless, when present, stroke in patients with PFO is hypothesized to involve paradoxical embolism. Patients with cryptogenic stroke are 5-fold more likely to have pelvic deep vein thrombosis compared with patients with stroke of determined origin, suggesting that a thrombotic substrate in the setting of an intracardiac shunt via a PFO is sufficient to mediate the risk of stroke.13 Alternatively, left atrial dysfunction resulting from chronic right-to-left shunt or anatomic features of an atrial septal aneurysm (ASA) that predispose to atrial fibrillation or decrease left atrial function are hypothesized to promote left atrial (appendage) thrombosis.14 The precise contribution of ASA or shunt magnitude to PFO-associated stroke risk, however, is unresolved.14,15

Management of PFO in Clinical Practice

Primary Prevention of Stroke

There are no universally accepted evidence-based recommendations for the medical, minimally invasive, or surgical treatment of PFO for the primary prevention of stroke. In a cohort analysis, the outcome of 14 165 patients undergoing cardiac surgery was analyzed retrospectively according to PFO status. In that study, 2277 patients were diagnosed with PFO, among whom 639 (28%) underwent defect closure as a secondary procedure to planned cardiac surgery. Repair of PFO was associated with an increased risk of in-hospital stroke (2.8% versus 1.2%), but no difference was observed with respect to long-term outcomes of all-cause mortality and stroke.16 Although some surgeons perform routine PFO closure in situations in which substantial postoperative right-to-left shunting is anticipated, clinical practice strategies vary.

Secondary Prevention of Stroke

Medical Therapy

The largest trial evaluating the optimal medical therapy for patients with PFO and a history of cryptogenic stroke was the Patent Foramen Ovale in Cryptogenic Stroke Study (PICCSS), in which 630 patients with a recent ischemic stroke were randomized to receive warfarin (international normalized ratio goal, 1.4–2.8) or aspirin 325 mg daily for 24 months.15 Patients enrolled in PICCSS were screened for PFO by TEE, which was found in 33.8% of participants. Compared with aspirin, warfarin did not significantly affect the rate of the primary end point of recurrent ischemic stroke or death resulting from any cause (9.5% in the warfarin group versus 17.9% in the aspirin group; P=0.28). Furthermore, in PICCSS, medically treated patients with PFO achieved the primary end point at the same rate as medically treated patients without PFO (14.3% versus 12.7%; P=0.65).15 A meta-analysis of >2500 patients supported these conclusions and demonstrated no increased risk of stroke recurrence in medically treated patients with or without PFO.17 Although there is insufficient evidence to determine whether anticoagulation is equivalent to aspirin, the use of antplatelet therapy to prevent recurrent stroke/TIA in PFO patients is a Class IIa recommendation, according to expert consensus guidelines,18 and is often used in clinical practice.

Percutaneous PFO Closure: Contemporary Clinical Trial Data Update

As a result of increased availability and low complication rates in the current era, percutaneous PFO closure has evolved as an attractive potential option to mitigate stroke risk due to paradoxical embolism (Figure 2). For example, in a meta-analysis of observational/retrospective studies, a reduction from 5 events per 100 patient-years in the medically treated group to 0.8 events per 100 patient-years in the PFO closure group was observed.19 Three contemporary trials in the field have been published recently (Table).1–3

CLOSURE I Trial

In the 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 Trial (CLOSURE I), 909 patients (age, 18–60 years) with a history of cryptogenic stroke/TIA and PFO detected by TEE were randomized to percutaneous PFO closure with the STARFlex septal closure system (NMT Medical Inc), followed by clopidogrel (75 mg/d) for 6 months and aspirin (81 or 325 mg/d) for 2 years, or medical therapy with warfarin or aspirin at the discretion of the treating physician.1 The primary end point was a composite of stroke or TIA during the 2-year follow-up period, all-cause mortality within 30 days of randomization, and neurological death from 31 days to 2 years after randomization. Features of PFO generally associated with increased stroke risk, such as ASA and moderate or large shunt magnitude, were well represented in the study population but were not predictive of stroke in this study.
Device implantation was successful in 89.4% of patients. The primary end point was achieved by 5.5% of patients in the PFO closure group and 6.8% of patients in the medical therapy group ($P=0.37$). Moreover, an increased adverse event rate may have offset the potential benefit of PFO closure in this trial: Major vascular complications and new-onset atrial fibrillation occurred in 3.2% and 5.7% of patients, respectively, in the PFO closure group, whereas only 0.7% of patients developed atrial fibrillation in the medical therapy group.

**PC Trial**

The Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder With Medical Treatment in Patients With Cryptogenic Embolism (PC Trial) enrolled 414 patients <60 years of age with PFO identified by TEE and history of ischemic stroke/TIA (identified by neuroimaging) or a clinically and radiologically confirmed extracranial peripheral thromboembolism. Akin to the CLOSURE I trial, high-risk PFO features were well represented in the cohort and were distributed evenly between treatment groups. Patients randomized to PFO closure, which was performed with the Amplatzer PFO Occluder device (St. Jude Medical), received aspirin (100–325 mg/d) for at least 6 months and ticlopidine (250 or 500 mg/d) or clopidogrel (75 or 150 mg/d) for 1 to 6 months. Patients in the medical therapy group were treated with aspirin, warfarin, clopidogrel, or aspirin/dipyridamole according to the recommendation of the treating physician. The primary end point was a composite of death, nonfatal stroke, TIA, or peripheral embolism during the mean follow-up period of $\approx4$ years.

Device implantation was successful in 95.9% of patients. Primary endpoint events occurred in 7 patients (3.4%) in the PFO closure group and 11 patients (5.2%) in the medical therapy group ($P=0.34$). Three patients (1.5%) had procedural complications, and atrial fibrillation developed in 6 patients (2.9%) in the closure group and 2 patients (1.0%) in the medical therapy group. Although the PC Trial is unique in that patients with peripheral paradoxical emboli were included, only 11 patients experienced these as their index event. Thus, a key limitation of the PC Trial was low patient enrollment.

**RESPECT Trial**

In the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) Trial, 980 patients (age, 18–60 years) with cryptogenic ischemic stroke and PFO identified by TEE were randomized to percutaneous PFO closure with the Amplatzer PFO Occluder or medical therapy. Patients in the PFO closure group received aspirin (81–325 mg/d) and clopidogrel (75 mg/d) for 1 month, followed by aspirin alone for 5 months, after which the antiplatelet regimen was determined by the treating physician. In the medical therapy group, patients were treated with aspirin, warfarin, clopidogrel, or aspirin/dipyridamole according to the recommendation of the treating physician. The PFO characteristics were similar between treatment groups: Approximately one third of patients had an ASA, and an intracardiac shunt of moderate or greater severity was present in two thirds of patients. The primary end point was a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization during the mean follow-up period of 2.6 years.

Despite similar baseline characteristics between treatment groups, the
Patients enrolled, n 909 414 980
Mean follow up time, y 2 4 2.6
Inclusion criteria (in addition to PFO diagnosed by TEE) Age=18–60 y, cryptogenic stroke or TIA

Antithrombotic regimen for patients in PFO closure group Aspirin (81 or 325 mg/d) for 2 y and clopidogrel (75 mg/d) for 6 mo
Aspirin (100–325 mg/d) for >5 mo and clopidogrel (75–150 mg/d) for 1–6 mo or ticlopidine (250–500 mg/d) for 1–6 mo
Aspirin (81–325 mg/d) for 6 mo and clopidogrel (75 mg/d) for 1 mo

Antithrombotic regimen for patients in medical treatment group Physician discretion: aspirin and/or warfarin
Physician discretion: aspirin, thiopropylidine, oral anticoagulation, or a combination thereof
Physician discretion: aspirin, warfarin, clopidogrel, or aspirin+dipyridamole

Primary end point Composite of stroke/ TIA, all-cause mortality at 30 d, and neurological death
Composite of death, nonfatal stroke, TIA, or peripheral embolism
Composite of nonfatal stroke, fatal stroke, or death within 45 d of randomization (or 30 d after device implantation)

Intention-to-treat analysis: primary endpoint events, n (%) Medical therapy: 29 (6.8)
PFO closure: 23 (5.5) (P=0.37)
Medical therapy: 11 (5.2)
PFO closure: 7 (3.4) (P=0.34)
Medical therapy: 16 (3.3)
PFO closure: 9 (1.8) (P=0.08)

Rate of atrial fibrillation, % Medical therapy: 0.7
Closure: 5.7 (P=0.001)
Medical therapy: 1.0
Closure: 2.9 (P=0.17)
Medical therapy: 1.5
Closure: 3.0 (P=0.13)

Device-related vascular complications, % 3.2
1.5
0.6

CLOSURE I indicates 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 Trial; PC, Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder With Medical Treatment in Patients With Cryptogenic Embolism; PFO, patent foramen ovale; RESPECT, Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; TEE, transesophageal echocardiography; and TIA, transient ischemic attack.

Device implantation was successful in nearly all patients. A total of 9 primary end points were reported for the PFO closure group compared with 16 in the medical therapy group, which corresponded to an overall event rate of 0.66 per 100 patient-years in the closure group and 1.38 events per 100 patient-years in the medical therapy group (P=0.08). Although a 2-fold increase in the rate of new-onset atrial fibrillation was observed in device-treated patients compared with the medical therapy group (P=0.13), failure of PFO closure to improve outcome was unlikely due to this or device-associated complications because, overall, the rate of adverse events was not significantly different between the treatment groups.

Subgroup Analyses
There was no clear association between shunt size or presence of ASA with stroke risk across each of the 3 trials. In the PC Trial, a trend toward benefit by PFO closure was observed in patients <45 years of age, which may suggest a stronger contribution of paradoxical embolism to overall stroke risk in younger patients compared with older patients, in whom competing causes of stroke are likely to be more prevalent.

Several factors may limit the accurate assessment of interventions that aim to prevent stroke in PFO patients. First, PFO-associated stroke risk is lifelong; thus, risk reduction analyses may require follow-up periods well beyond the 2- to 4-year time frame studied in recent clinical trials. Second, PFO-associated stroke is a low event rate occurrence, which introduces practical concerns for the completion of sufficiently powered, controlled, clinical trials in this disease. Third, patients at elevated risk for paradoxical embolism may not be available for clinical trial enrollment because of the off-label use of percutaneous PFO closure devices.

Summary
Three recent clinical trials investigating the benefit of percutaneous PFO closure for the secondary prevention of stroke did not demonstrate a significant reduction in recurrent events. Therefore, antplatelet agents or systemic anticoagulants are recommended for secondary stroke prevention in this patient population. PFO closure remains reasonable, however, for patients with multiple paradoxical embolus/cryptogenic emboli despite appropriate antplatelet or antithrombotic regimens, selected scuba divers, patients with platypnea-orthodeoxia syndrome, or patients with chronically elevated right heart pressures.

Management of Presented Case
In the case vignette patient, PFO was diagnosed in the setting of submassive pulmonary emboli and paradoxical embolism with acute left axillary artery thrombosis. On the basis of data from 3 recently published, randomized, clinical trials involving stroke prevention in PFO patients, a medical therapeutic strategy was favored over percutaneous...
PFO closure to prevent recurrent paradoxical embolism. Treatment with rivaroxaban was initiated at a dose of 15 mg twice daily for 3 weeks, followed by 20 mg daily thereafter. At 2 months after the index event, the patient reported no recurrence of symptoms or drug therapy side effects.

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References
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