Review

Patent Foramen Ovale and Stroke

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A patent foramen ovale (PFO) is a frequent remnant of embryological development with clinical importance in thromboembolism, paradoxical embolism, stroke, platypnea-orthodeoxia, decompression sickness, and migraine headache. The proposed mechanisms of stroke with PFO include paradoxical embolization, in situ thrombosis within the canal of the PFO, associated atrial arrhythmias, and concomitant hypercoagulable states. Prospective trials using aspirin treatment to reduce recurrent stroke showed a significant recurrence of neurologic events in patients with a PFO and atrial septal aneurysm. Use of warfarin anticoagulation does not further reduce recurrent stroke rates compared with antiplatelet therapy. Both surgical and catheter-based modes of closure have been shown to decrease the rate of subsequent embolic events substantially. Successful closure, defined by transesophageal echocardiography, appears to predict freedom from subsequent embolic events. To our knowledge, no randomized trials comparing anticoagulation with surgical or catheter-based closure have been performed.

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ASA = atrial septal aneurysm; CI = confidence interval; CVA = cerebrovascular accident; INR = international normalized ratio; MRI = magnetic resonance imaging; OR = odds ratio; PFO = patent foramen ovale; RLS = right-to-left shunt; TEE = transesophageal echocardiography; TIA = transient ischemic attack; WARSS = Warfarin-Aspirin Recurrent Stroke Study

A patent foramen ovale (PFO) is a frequent remnant of embryological development[1] with clinical importance in thromboembolism, paradoxical embolism, stroke, platypnea-orthodeoxia, decompression sickness, and migraine headache.[2] Although a case report in 1930 described in detail a patient who died of a stroke with a large thrombus straddling a PFO, the pathologic role of this interatrial communication in cerebrovascular events has only been of recent interest.[3-7] This article surveys scientific knowledge to delineate the relationship of PFO to stroke and focuses on the many aspects of this embryological defect.

DEVELOPMENTAL ANATOMY

By 33 days of intrauterine growth, the septum primum begins to form from the roof of the atrium and encroach on the left endocardial cushion. The initial opening between the right and left atrium, the ostium primum, is closed by fusion of the septum primum to the endocardial cushion. Patency between the right and left atrium remains through a coalescence of fenestrations within the septum primum. This subsequent passage located in the mid portion of the interatrial septum becomes the ostium secundum. During the sixth week of gestation, the septum secundum grows downward from the roof of the atrium and fuses with the endocardial cushions. The septum secundum overlaps the ostium secundum. Incomplete growth within the septum secundum results in the formation of the foramen ovale. By the early seventh week of gestation, the juxtaposition of the septum primum with the septum secundum allows for a unidirectional (right-to-left) flow of intrauterine oxygenated blood traveling from the inferior vena cava, through the foramen ovale and the ostium secundum, and into the left atrium (Figures 1 and 2).

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At birth or shortly after, the septum primum and the septum secundum usually fuse, closing the interatrial septum to the flow of blood. Ostium primum atrial septal defects occur when the septum primum fails to fuse with the endocardial cushion. Ostium secundum atrial septal defects occur when there is excess resorption of septum primum or inadequate development of septum secundum. A PFO persists when fusion of the septum primum with the septum secundum is inadequate.[8]

DIAGNOSIS OF PFO AND ASSOCIATED STRUCTURES

The prevalence of PFO depends somewhat on the means used to define it. In a study of 965 autopsy patients, a PFO was found in 27.3% of the hearts; however, this progressively declined from 34.3% in the first 3 decades to 20.2% in the ninth and tenth decades of life. It was noted, however, that the size became slightly larger with age, increasing from 3.4 mm in the first decade to 5.8 mm in diameter by the 10th decade of life.[1]

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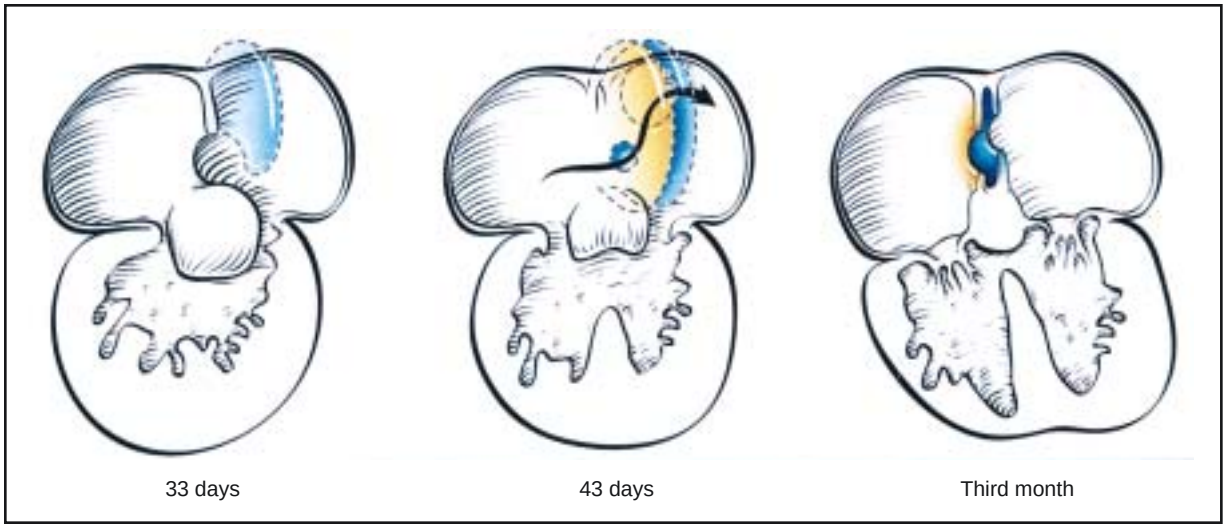

Figure 1. Early atrial developmental anatomy up to 3 months of gestation. The arrow indicates the shunting of blood through the foramen ovale and the ostium secundum and into the left atrium.

The presence of a PFO has been delineated noninvasively with use of echocardiography. Essentially, a PFO is suggested by the presence of echo dropout in the atrial septum visualized in more than 1 plane (Figure 3). The appearance of microbubbles in the left atrium within 3 to 5 cardiac cycles after injection of agitated saline peripherally is considered diagnostic of PFO with associated right-to-left shunt (RLS). Grading of the RLS of the PFO is arbitrary. Ten bubbles are considered trivial, more than 10 bubbles indicate a small shunt, and intense pacification of the left atrium suggests a large shunt.[5] The diagnosis of PFO is enhanced with multiple intravenous contrast injections with maneuvers that cause transient elevations of right atrial pressures (cough, Valsalva) to enhance the RLS.[9]

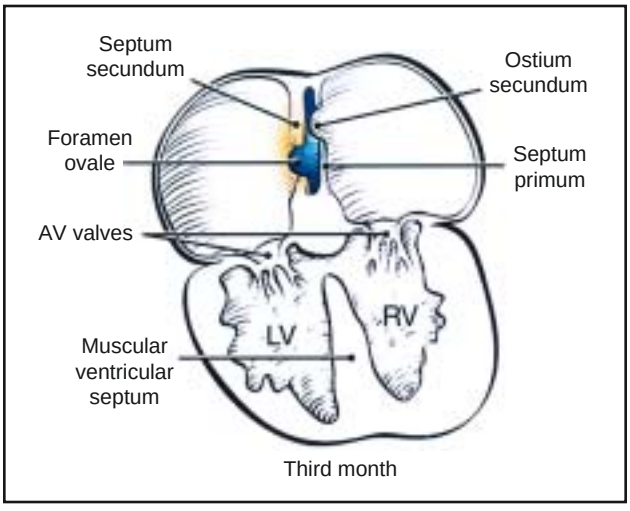

Figure 2. Embryological cardiac development at 3 months of gestation. AV = atrioventricular; LV = left ventricle; RV = right ventricle.

An atrial septal aneurysm (ASA) is associated with a PFO.[2,4] Independently, in one autopsy series, 16 aneurysms (1%) of the septum primum were found among 1578 adults.[10] An ASA is defined by echocardiography as a bulging in the region of the fossa ovalis. Septum membrane mobility is determined by the sum of excursions at rest, essentially the greatest leftward and rightward deflections of the septum primum with respect to a perpendicular line to the fossa ovalis plane into either the left or right atrium (Figure 4). The amount of septal excursion to meet this definition is arbitrary, although a sum of 15 mm or more has been suggested.[11] In an adult study involving 195 patients with an ASA, the ASA was an isolated structural defect in 62 patients (32%). However, in 65 patients (33%), there was an associated PFO with interatrial shunting.[12]

TRANSESOPHAGEAL ECHOCARDIOGRAPHY COMPARED WITH TRANSCRANIAL DOPPLER SONOGRAPHY

To date, transesophageal echocardiography (TEE) is considered the most sensitive method to detect PFO. Transcranial Doppler sonography of the middle cerebral artery during contrast injection has been proposed as an alternative method for detecting a PFO. Essentially, a PFO is suggested by the appearance of microbubbles in the middle cerebral artery after injection of agitated saline peripherally. Heckmann et al[13] described 45 patients with stroke or transient ischemic attacks (TIAs) in whom both transcranial Doppler sonography and TEE were performed

to detect a PFO as a mechanism for embolic cerebral ischemia. Both TEE and transcranial Doppler sonography were performed in all patients. When a PFO was found by TEE and/or transcranial Doppler sonography, it was classified as positive. When transcranial Doppler sonography results were positive but TEE results were negative, a second TEE was performed and vice versa. A PFO was found with one test or the other in 26 patients. The first TEE detected a PFO in 24 patients (sensitivity, 92.3%). The first transcranial Doppler testing detected a PFO in 22 patients (sensitivity, 84.6%). However, a transcranial Doppler sonogram detected a PFO in 2 patients in whom the first TEE result had been negative, leading to a second TEE, which confirmed PFO and revealed minimal shunting. In 4 patients in whom a transcranial Doppler sonogram result was negative, TEE detected a PFO. A second transcranial Doppler study confirmed shunting in 2 of these 4 patients. The investigators concluded that these 2 tests were useful in evaluating all patients with a suspected PFO and that the rate of detection was higher when using both than with a single test independently.[13] This finding also suggests that both tests are dependent on technical expertise.

STROKE EPIDEMIOLOGY

Stroke ranks as the third leading cause of mortality in the United States. Approximately 700,000 new strokes occur annually, accounting for more than $50 billion in lost productivity and total health care costs.[14] The etiology of a stroke is either hemorrhagic or ischemic. However, approximately 40% of ischemic strokes have no clearly definable cause and are termed *cryptogenic* strokes.[15] Furthermore, data from the Northern Manhattan Stroke Study[16] reported recurrence rates for all stroke subtypes of 9.4% per year and 10% for cryptogenic stroke.

Lechat et al[5] were the first to report an unusually high prevalence of PFOs in patients who had cryptogenic strokes. They studied the prevalence of PFO, detected by contrast surface echocardiography, in a population of 60 adults younger than 55 years with ischemic stroke. A PFO was found in 40% of the study population compared with 10% of a control group without stroke ($P<.001$). In addition, a PFO was present in 54% of patients with cryptogenic stroke ($P<.10$). Recently, Mas et al[3] prospectively evaluated patients between the ages of 18 and 35 years who presented with a stroke of unknown origin. Within a population of 598 patients, 216 (36%) had a PFO, 10 (1.7%) had an ASA, and 51 (8.5%) had both abnormalities. In addition, the association between PFO and stroke is stronger in certain subgroups. A meta-analysis of 9 studies showed that the overall rate of stroke was significantly associated with younger patients (≤55 years) who had a PFO (odds ratio [OR], 3.10; 95% confidence interval [CI], 2.29-4.21),

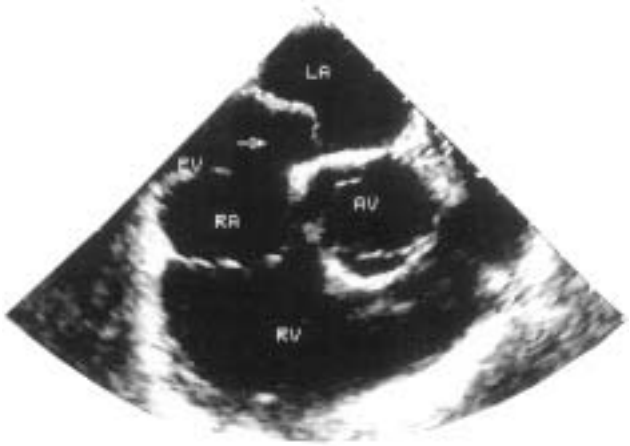

Figure 3. Transesophageal echocardiogram of a patent foramen ovale (arrow). AV = aortic valve; EV = eustachian valve; LA = left atrium; RA = right atrium; RV = right ventricle.

ASA (OR, 6.14; 95% CI, 2.47-15.20), and PFO plus ASA (OR, 15.59; 95% CI, 2.83-85.97).[17] A similar association was not found in older patients (≥55 years).

Despite the high prevalence of PFO in the general population, the actual stroke event rate remains small. It is unclear why there is not a more straightforward relationship between embryonic pathologic findings and stroke as a long-term outcome. This may be due in part to a relative lack of understanding of the pathophysiology of PFO and cryptogenic stroke in general.

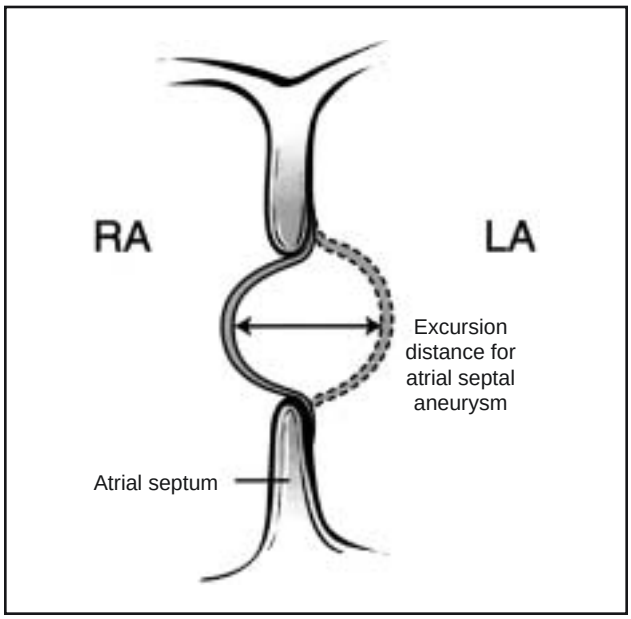

Figure 4. Atrial septal aneurysm. LA = left atrium; RA = right atrium.

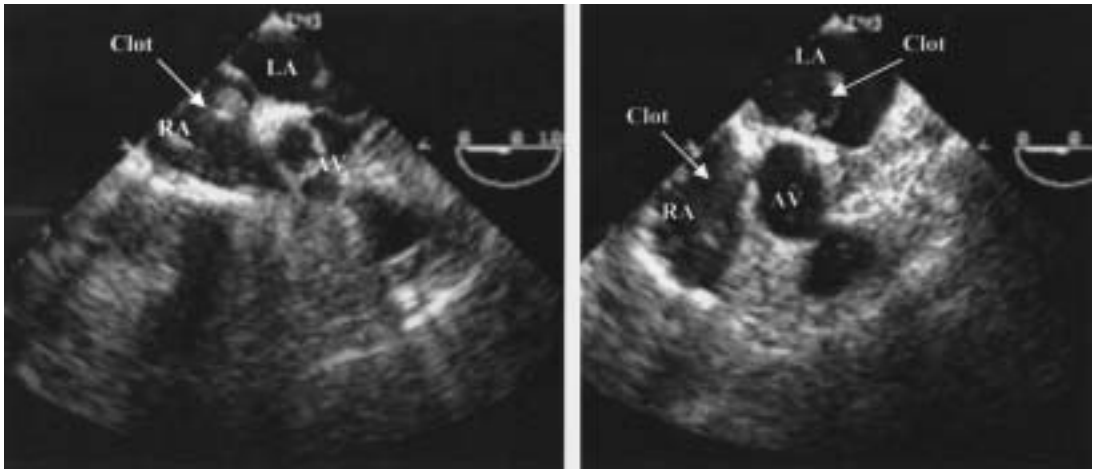

Figure 5. Transesophageal echocardiograms of a clot (arrows) traversing a patent foramen ovale. AV = aortic valve; LA = left atrium; RA = right atrium.

PARADOXICAL EMBOLI

Paradoxical embolism of thrombus, fat, and air through a PFO is a well-recognized complication.[18] The RLS across a PFO can occur during coughing, after the release phase of the Valsalva maneuver, during mechanical ventilation, and with elevated right atrial pressures resulting from pulmonary embolism, chronic lung disease, and right ventricular failure.[18]

Paradoxical emboli have been suggested as the main mechanism of stroke in patients with a PFO (Figure 5). Ranoux et al[19] tested the validity of this theory. In 68 consecutive patients younger than 55 years who presented with an ischemic stroke, a PFO was found in 32 patients (47%). A Valsalva-provoking activity that may induce an RLS was present at stroke onset in 6 patients with a PFO and in 8 patients without a PFO (P=.10). Clinical or radiological evidence of deep thrombosis was present in one patient with a PFO and none of the others. The investigators concluded that paradoxical embolization as the primary mechanism of stroke in patients with a PFO was not valid. Although the role of a PFO as a mechanism of paradoxical embolism and stroke is recognized, it remains a diagnosis of exclusion because direct demonstration of embolus passage through the PFO is rare.[20,21]

A second proposed mechanism for clot embolization is primary thrombus formation within the PFO canal formed as a consequence of stasis and minimal pressure differences between the atria (Figure 6). However, these data are anecdotal and typically based on surgical observations.[21,22]

SIZE AND SHUNTING CHARACTERISTICS

The morphologic and functional characteristics of a PFO assessed by TEE may be helpful in estimating the likelihood of paradoxical emboli. Hausmann et al[23] studied 78 patients with PFO and subdivided these patients into 3 groups. Group 1 consisted of 21 patients with stroke and evidence of paradoxical embolism. Group 2 had 30 patients with stroke and no evidence of paradoxical embolism. Group 3 had 27 patients without stroke. All patients were studied with contrast TEE, and the degree of left atrial filling was defined. On average, group 1 had 52% filling of the left atrium associated with the 7.1-mm opening of the PFO. Group 2 had 35% filling of the left atrium associated with a 4.4-mm average opening of the PFO. Group 3 had 23% filling of the left atrium associated with a 3-mm average opening of the PFO. The authors concluded that shunting is more severe and PFOs are larger in patients with strokes caused by paradoxical emboli.

Homma et al[24] studied 74 consecutive patients referred for ischemic stroke and classified these patients into 2 groups: determined origin vs cryptogenic strokes. All patients were studied with TEE, and the separation of the septum primum from the septum secundum was measured and the number of micobubbles appearing in the left atrium counted. On average, patients with stroke of known origin had a 0.6-mm opening with 1.6 microbubbles in the left atrium compared with patients with cryptogenic stroke who had a 2.1-mm opening corresponding to 16 microbubbles in the left atrium. These authors concluded that patients with cryptogenic strokes had larger PFOs with more extensive RLS than patients with stroke of determined cause.

In addition to PFO, ASA is a putative risk factor for cardiac embolisms. Agmon et al[25] sought to determine the frequency of ASA in the general population and to compare the frequency of ASA in patients with cerebral ischemic

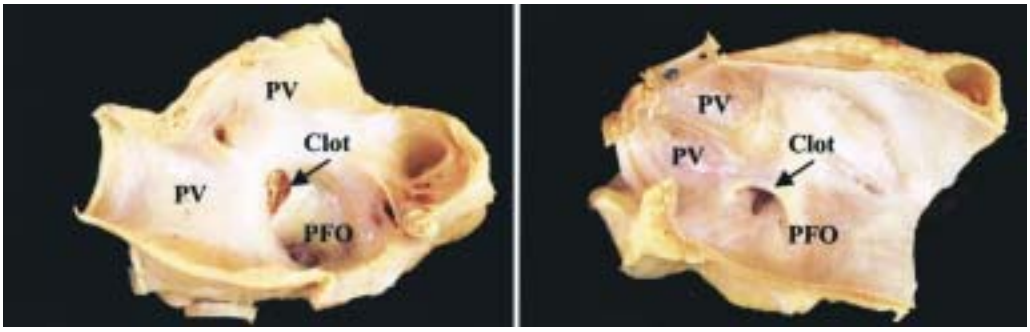

Figure 6. Autopsy specimen of a clot (arrow) passing through a patent foramen ovale (PFO). PV = pulmonary vein. Photograph courtesy of William D. Edwards, MD, and Dylan V. Miller, MD, Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, Minn.

events. They noted that the frequency of ASA was 7.9% in patients with stroke vs 2.2% in control subjects. A PFO was detected with contrast injections in 56% of patients with ASA. In 86% of patients with ASA and cerebral ischemia, TEE did not detect an alternative source of cardiac embolisms other than an associated PFO. These data suggest that ASA is frequently associated with PFO and that paradoxical embolisms are the mechanism of embolic stroke.

De Castro et al[26] studied 350 consecutive patients with acute ischemic stroke or TIA using contrast TEE and attempted to define high-risk vs low-risk anatomy to identify patients at risk for subsequent stroke. They concluded that patients with PFO and ischemic stroke were at high risk for recurrence if they had an RLS at rest or high septum membrane mobility determined by the sum of excursions at rest. Overall, the risk of recurrent stroke or TIA at 3 years of follow-up was 4.3% for those with the low-risk PFO pattern compared with 12.5% for those with a high-risk PFO pattern (P=.05). Although the mechanism is unknown, the increased mobility of the fossa ovalis membrane in patients with a PFO may play an important role in allowing paradoxical shunt via a mechanical action of a wind-sail motion in directing inferior vena cava blood flow through the intra-atrial conduit.[26]

ATRIAL ARRHYTHMIA AS SUBSTRATE FOR EMBOLI

Berthet et al[27] tested the hypothesis of whether paroxysmal atrial arrhythmia (resulting from abnormal atrial septal anatomy) could be another cause of thrombosis formation and subsequent embolization to the brain. They studied 62 consecutive patients younger than 55 years who had ischemic stroke of unknown cause and TEE evidence of ASA or PFO. These patients underwent an electrophysiology study for assessment of the inducibility of sustained atrial fibrillation with use of programmed atrial stimulation. The authors noted atrial vulnerability in 58% of patients with and in 25% of patients without atrial septal abnormalities (OR, 4.1; 95% CI, 1.3-12.7; P<.02). This suggests a potential role of transient atrial arrhythmia in thrombosis formation in the presence of patients with atrial abnormalities.

HYPERCOAGULABLE STATES

Coagulation abnormalities may promote paradoxical emboli in patients with PFO and cryptogenic stroke. Chaturvedi[28] studied 17 patients who presented with cryptogenic stroke and a PFO. A complete hematologic evaluation was performed in 16 patients. Hemostatic abnormalities were present in 5 (31%) of 16 patients, including abnormal activated protein C resistance in 4 and elevated anticardiolipin antibody levels in 2 (1 also had activated protein C resistance). In comparison, an additional 22 patients underwent TEE for either stroke or TIA symptoms, and 3 (14%) of 22 patients without a PFO had evidence of hypercoagulability—2 patients had positive anticardiolipin antibodies and 1 had activated protein C resistance. All patients with an identified hypercoagulable disorder underwent anticoagulation with no reported stroke recurrence after 20 months. Although this study is small, it suggests hypercoagulability might be more prevalent in patients with PFO and stroke. A better understanding of the potential mechanisms of PFO and cryptogenic stroke is required. With an improved understanding, targeted therapies can be developed in an effort to improve long-term outcomes.

MEDICAL TREATMENT OF PATIENTS WITH PFO AND STROKE

The role of medical therapy in patients with PFO and stroke has not been studied extensively. To our knowledge, no studies comparing medical, surgical, and/or catheter-based trials have been performed. Medical therapy to date has included either antiplatelet or antithrombin drugs. Comess et al[29] described 33 patients with PFO and presumed paradoxical embolism who were followed up for 18 months but

did not undergo medical therapy or surgical intervention and reported a recurrent event rate of 16% per year (combined end point of TIA and cerebrovascular accident [CVA]). In a retrospective study by Mas et al[30] in 132 patients younger than 60 years with PFO and cryptogenic stroke, patients were treated with either aspirin (250-500 mg/d) or oral anticoagulation (target international normalized ratio [INR], 2.0-3.0). The average annual rate of recurrence was 1.2% for CVAs and 3.4% for the combined end point of TIA and CVA. Similar recurrence rates with medical treatment were reported from the Lausanne Stroke Registry.[31] Ninety-two patients with PFO and cryptogenic stroke were treated with aspirin (250-500 mg/d), whereas 37 patients were treated with oral anticoagulation (target INR, 2.0-3.0). In 8 patients, the regimen was switched to aspirin after 3 months of oral anticoagulation. The mean annual recurrence rate was 1.9% for CVA and 3.8% for the combined end point of TIA and CVA during a follow-up period of 3 years, with no statistically significant difference between the 2 antithrombotic drug regimens.

Mas et al[3] prospectively assessed the risk of recurrent cerebrovascular events associated with septal disorders in young people who were receiving aspirin (300 mg/d) for secondary prevention. After 4 years, the reported recurrence rate of stroke was 2.3% in patients with a PFO, 0% in patients with an ASA, and 4.2% in those with both a PFO and an ASA. At 4 years, the risk of stroke or TIA in the group of patients with a PFO and an ASA was 19.2%.[3] Hence, aspirin did not offer protection for these high-risk patients.

The Warfarin-Aspirin Recurrent Stroke Study (WARSS) was a prospective trial that randomized 2206 patients with ischemic stroke to either aspirin (325 mg/d) or warfarin (target INR, 1.4-2.8). This 2-year trial found no difference between the 2 therapies regarding end points of recurrent stroke or death. This trial also randomized 578 patients with cryptogenic stroke and found no therapeutic advantage of warfarin over aspirin.[32]

Subsequently, the PFO in Cryptogenic Stroke Study (PICSS) evaluated TEE findings in 630 patients with cryptogenic stroke within the WARSS trial. Among the patients with TEE images adequate for PFO analysis, a PFO was found in 39% of patients with cryptogenic stroke compared with 29.9% in patients with known cause of stroke ($P<.02$). Large PFOs were found in 20.0% of patients with cryptogenic stroke compared with 9.7% in those with a known stroke origin ($P<.001$). When the efficacy of warfarin was compared with that of aspirin, there was no significant difference in the incidence of stroke or death. The size of the PFO and the presence of ASA did not influence these data.[33]

SURGICAL CLOSURE OF PFO

Because a PFO represents a surgically repairable lesion, interest in open closure has been substantial. Homma et al[34] described 28 patients with cryptogenic stroke and a PFO detected by TEE who underwent PFO closure by open thoracotomy. All patients selected for surgery refused, could not take, or failed warfarin therapy. At 19-month follow-up after an uneventful postoperative course, 4 patients (14%) experienced neurologic event recurrence: 1 with stroke and 3 with TIAs. None of the 17 patients younger than 45 years experienced recurrence, whereas 4 (35%) of 11 patients 45 years or older experienced a recurrence of a neurologic event ($P<.02$). The authors concluded that, although a PFO is easily repairable in patients with cryptogenic stroke, its closure does not consistently prevent recurrence of ischemic events. Furthermore, the recurrence rate was higher in older patients with cryptogenic stroke (relative risk of 2.76 per 10 years; 95% CI, 1.07-7.16).

In contrast, Dearani et al[35] retrospectively analyzed 91 patients to determine the outcome of surgical closure of PFO in patients with prior ischemic neurologic events to define the rate of stroke or TIA recurrence and to identify risk factors for these recurrences. All their patients underwent successful surgical closure (suture in 82, patch closure in 9) with a 2-year follow-up. They found that the overall freedom from TIAs and strokes was 92.5% at 1 year and 83.4% at 2 years. Of the many patient demographic and preoperative variables analyzed, only multiple neurologic events before PFO closure was a significant risk factor for TIA or stroke recurrence by univariate analysis ($P=.05$).

In a study of surgical closures of PFO, Devuyst et al[36] prospectively examined 30 patients with stroke and PFO who were believed to be at high risk for recurrence. The patients were younger (<60 years) and had to meet 2 of the 4 following criteria: recurrent clinical cerebral vascular events or multiple ischemic lesions on brain magnetic resonance imaging (MRI), a PFO associated with an ASA, more than 50 microbubbles counted in the left atrium on contrast TEE, and Valsalva maneuver or cough preceding the stroke. The patients underwent direct suture of PFO while undergoing cardiopulmonary bypass. All patients then underwent brain MRI and TEE with simultaneous transcranial Doppler ultrasonography after contrast injection to ensure resolution of the interatrial shunt. After a mean follow-up of 2 years without antithrombotic treatment, no cerebral vascular events had recurred, and no new lesions had developed on MRI.

TRANSCATHETER CLOSURE OF PFO

Because of the morbidity of open heart surgery, catheter-based approaches to PFO are an attractive alternative (Fig-

ure 7). Braun et al[37] reported a series of 276 consecutive patients with a PFO and history of 1 thromboembolic event who underwent percutaneous PFO closure with a PFO-star device. The implantation was successful in all 276 patients, although complicated by transient ST elevation in 1.8% of the patients and a TIA in another 0.8% of the study population. After approximately 15 months of follow-up, 0% had recurrent stroke, 1.7% sustained a TIA, and 0% developed peripheral emboli.

A second study by Hung et al[38] evaluated the use of transcatheter PFO closure for patients with paradoxical embolism. Data were collected from patients after PFO closure with the clamshell septal occluder (Clamshell Septal Umbrella) (C. R. Bard, Inc, Billerica, Mass), CardioSEAL septal occluder (NMT Medical, Inc, Boston, Mass), or buttoned devices (Custom Medical Devices, Amarillo, Tex) at 2 institutions. Sixty-three patients were followed up for an average of 2.6 years. Fifty-four (86%) had effective closure of the PFO (trivial or no residual shunt by echocardiography), whereas 7 (11%) had mild and 2 (3%) had moderate residual shunting. There were 4 recurrent embolic neurologic events after device placement (1 stroke and 3 TIAs). Two of the 4 neurologic events were associated with suboptimal device performance (one patient had a significant residual shunt and another patient had a "friction lesion" in the left atrial wall associated with a displaced fractured device arm). The device was well seated in the other 2 patients with normal function. The risk of recurrent stroke or TIA after device placement was 3.2% per year for all patients.

Windecker et al[39] treated 80 patients with PFO and at least 1 paradoxical embolic event. Patients received 1 of 5 different PFO-closure devices. Sixty patients had a PFO only, whereas 20 patients had both a PFO and an ASA. The implantation procedure was successful in 78 patients (98%). Complete PFO closure as assessed by color flow imaging and/or bubble contrast injection under Valsalva maneuver was achieved in 57 (73%), and a residual RLS of some degree was present in 21 (27%). During 5 years of follow-up, the actuarial annual risk for an embolic event was 2.5% for TIA, 0% for CVA, 0.9% for peripheral emboli, and 3.4% for the combined end point of TIA, CVA, and peripheral embolism. A postprocedural shunt was a predictor of recurrent paradoxical embolism with a relative risk of 4.2 (95% CI, 1.1-17.8; P=.03). The risk for recurrent embolic events in patients with both ASA and PFO was not significantly increased compared with patients with only PFO. The risk of recurrence was highest during the first year after PFO closure, with no further events beyond 2 years after PFO closure.

Recently, Martin et al[20] reported the immediate and long-term outcome in 110 consecutive patients who underwent transcatheter closure of PFO because of paradoxical embolism. Procedural success with successful device deployment without shunt was achieved in all the patients. One device migrated early, requiring surgical intervention (0.9%), and 1 device placement led to cardiac tamponade, requiring pericardiocentesis. Long-term follow-up of 2.3 years revealed 2 patients who experienced recurrent neurologic events (1 fatal stroke and 1 TIA) and 4 patients (3.6%) who required reintervention for device malalignment or significant shunt. A Kaplan-Meier analysis showed a freedom from recurrent embolic events and reintervention of 96% and 90% at 1 and 5 years, respectively.

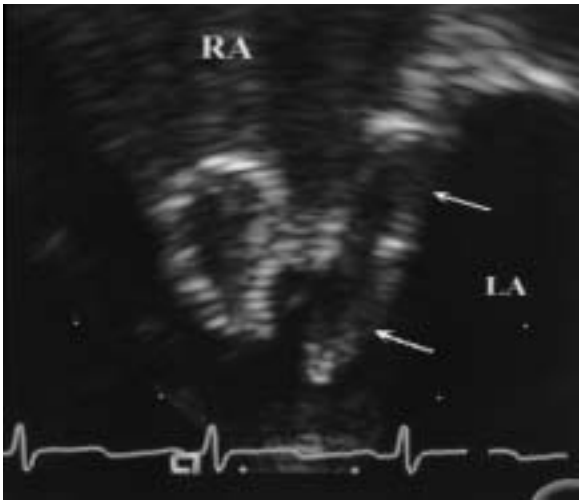

Figure 7. Transesophageal echocardiogram of an Amplatzer percutaneous closure device (arrows). LA = left atrium; RA = right atrium. Photograph courtesy of Naser M. Ammash, MD, Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, Minn.

PFO AND SPORT DIVERS

PFOs have been found in high frequency in divers with a history of decompression sickness and with evidence of brain lesions on MRI. Schwerzmann et al[40] compared MRI and TEE in 52 sport divers with 52 healthy nondiving controls. They found that divers with a PFO had a 4.5-fold increase in decompression illness events and 2 times more ischemic brain lesions than divers without PFO. In addition, Reul et al[41] found hyperintense lesions of the subcortical cerebral white matter in 27 (52%) of 52 divers who had a total of 86 focal hyperintensities compared with 10 (20%) of 50 controls with 14 focal hyperintensities (P<.01). These central nervous system lesions in amateur divers with a PFO were believed to be potentially secondary to paradoxical arterial gas embolism during decompression. Additionally, Knauth et al[42] used transcranial Doppler ultrasonography to detect an RLS in 87 sport

divers. They reported that multiple brain lesions on MRI occurred exclusively in those with a shunt, presumed to be from a PFO.

PFO AND MIGRAINE HEADACHES

A relationship between migraine with aura and cardiac RLS has been reported. Del Sette et al[43] performed a case-control study to assess the association between PFO and patients with migraines. They evaluated 44 patients with migraine with aura, 73 patients younger than 50 years with focal cerebral ischemia, and 50 controls (asymptomatic for cerebrovascular disease with no history of migraine). Right-to-left shunt was evaluated by transcranial Doppler sonography with injection of intravenous contrast medium. They found that 18 (41%) of 44 migraine patients showed RLS compared with 8 (16%) of 50 controls ($P<.001$). Twenty-six patients (35%) with cerebral ischemia had RLS. They concluded that the prevalence of RLS in patients with migraine with aura is significantly higher than in healthy controls and is similar to the prevalence of RLS in young patients with stroke.

Wilmshurst et al[44] studied 37 patients who underwent PFO closure for various indications. A consultant neurologist unaware of information about residual shunt interviewed the patients. Of these patients, 21 (57%) had a history of migraine before the procedure (with aura in 16, without aura in 5). During a 30-month follow-up, 7 individuals who had previously had migraine with aura and 3 who had previously had migraine without aura reported no migraine symptoms. Eight patients with prior migraine with aura before closure reported a decrease in frequency and severity of migraines. Three reported no alteration in migraine episodes. The authors suggested a causal association between RLS and migraine with aura. They speculated that PFO closure could be performed in selected patients with severe migraines to improve or abolish symptoms.

CLINICAL APPROACH

Patients who present with a potential embolic or cryptogenic stroke require extensive evaluation for an embolic source. A history may assist in diagnosis, such as platypnea-orthodeoxia or onset of symptoms at the time when an RLS may have been provoked, such as with a Valsalva-type maneuver. Furthermore, a history of pulmonary disease that may lead to RLS, such as chronic obstructive pulmonary disease, pulmonary hypertension, or chronic pulmonary emboli, should be obtained. Additionally, when an arterial embolus is suspected, rigorous exclusion of deep venous thrombosis is required. If the patient has a history of prior thromboembolic disease and this represents a second event or a single event without provocation, an evaluation of hypercoagulability should be pursued. A cardiac evaluation to look for a source of the embolic event or RLS is an important component of the initial investigation. A TEE with contrast injections is a reliable and confirmed tool for diagnosing PFO, although transcranial Doppler sonography is an excellent alternative if TEE is unavailable.

The management of a cryptogenic stroke in a patient with PFO is evolving with additional studies and improved treatment techniques. Meier and Lock[45] concluded that the only definitive indication for PFO closure is recurrent paradoxical embolism in the presence of a PFO with an associated ASA and recommended that a percutaneous approach should precede surgical intervention because of the low risk of the procedure and favorable long-term outcomes. Given the failure of both aspirin and warfarin to prevent strokes in this group, this recommendation seems straightforward.[32] As further clinical studies become available, the risk-benefit analysis for closure in other subsets of patients will likely broaden. If the patient's cryptogenic stroke represents a second event suggestive of a paradoxical embolus, then PFO closure should be performed. In patients in whom the stroke is the first event, there are no guidelines to direct therapy. One approach is to identify patients at high risk for subsequent events as candidates for PFO closure (determined, for example, by the presence of a eustachian valve directed toward the PFO, the gaping diameter of the PFO, and the number of microbubbles present in the left atrium during the first seconds after release of a Valsalva maneuver during a bubble test).[24,45] Although surgical and percutaneous methods have not been compared directly, the procedure time, invasiveness, and patient convenience suggest that a percutaneous approach should be the first option.

Current recommendations for therapy after percutaneous closure, based on primarily observational data, vary considerably. Studies have suggested that the risk of stroke recurrence is greater in the first year after percutaneous closure.[20,39] Therefore, it appears that a more intensive antiplatelet or anticoagulation regimen may be required early during the first year after device placement before there is complete reendothelialization of the device and/or while patients remain at high risk of subsequent stroke.[16,46] Currently, investigators who have placed a percutaneous closure device have prescribed aspirin (81-325 mg/d) for discharged patients and required subacute bacterial endocarditis prophylaxis for 6 months. However, whether anticoagulation should persist after endothelialization remains to be determined. In a recent review, Meier and Lock[45] advocated that a follow-up TEE be performed a few months after device placement to ascertain whether a tight closure of the PFO exists, without evidence of thrombus. If this condition were present,

it would provide justification for cessation of anticoagulation treatment.

In a study by Martin et al,[20] the need for additional anticoagulation treatment beyond antiplatelet therapy was determined by preexisting patient risk. First, patients who required ongoing anticoagulation for other causes, such as pulmonary embolism, deep venous thrombosis, or known hypercoagulable states with previous clotting, were discharged with low-molecular-weight heparin until therapeutic anticoagulation with warfarin was achieved. Second, patients with a hypercoagulable state, defined as having 1 embolic event and a risk factor for clotting that could be eliminated, received 3 to 4 months of warfarin anticoagulation in addition to aspirin after device placement and were then switched to aspirin at standard doses. Third, patients with a hypercoagulable state, defined as having a history of more than 2 embolic events, and those with an arterial hypercoagulable state regardless of the presence of an associated risk factor for clotting at the time of paradoxical embolism were prescribed lifelong warfarin anticoagulation.[19]

CONCLUSION

Stroke is a common cause of morbidity and mortality. Approximately 40% of ischemic strokes are cryptogenic, and current research supports a causal relationship between cryptogenic stroke and PFO. Mechanisms of stroke with PFO include paradoxical embolization, in situ thrombosis within the canal of the PFO, associated atrial arrhythmias, and concomitant hypercoagulable states. The initial approach and management of patients who present with a cryptogenic stroke and PFO have been reviewed. The long-term results of medical therapy to prevent subsequent strokes in patients with a PFO have been primarily discouraging. Both surgical and catheter-based modes of closure have been shown to decrease the rate of subsequent embolic events substantially. Surgical and percutaneous methods have not been directly compared. However, the percutaneous approach appears less invasive and so successful that it seems to be a reasonable first choice. We expect the current indication of recurrent paradoxical embolism in the presence of a PFO associated with an ASA for PFO closure to broaden with further studies.

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