

Patent foramen ovale and cerebrovascular diseases

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SUMMARY

Patent foramen ovale (PFO) has been linked to ischemic strokes of undetermined cause (cryptogenic strokes). PFO—a remnant of fetal circulation when the foramen ovale does not seal after birth—can permit microemboli to escape the pulmonary filter into the intracranial circulation, causing stroke. Coexistent atrial septal aneurysm, pelvic deep vein thrombosis and inherited clotting factor deficiencies could potentiate stroke risk in patients with PFO. Transcatheter PFO closure, a minimally invasive procedure, is one technique used to prevent recurrent cerebrovascular events. A connection between PFO and migraine headache has been conceptualized from retrospective evidence of reduced migraine frequency and severity after PFO closure; however, prospective randomized trials are needed to verify the efficacy of PFO closure on migraine prevention. In this review we discuss embryologic origins, diagnostic techniques and treatment options for prevention of paradoxical embolism thought to be related to PFO, and the relation of PFO to cryptogenic stroke and migraine.

KEYWORDS cryptogenic stroke, migraine headache, paradoxical embolism, patent foramen ovale, transcatheter closure

REVIEW CRITERIA

A search for original articles published between 1985 and 2005 and focusing on patent foramen ovale was done in MEDLINE and PubMed. The search terms used were “patent foramen ovale”, “cryptogenic stroke”, “transcatheter patent foramen ovale closure” and “migraine relief after patent foramen ovale closure”. All papers identified were English language, full-text papers. We also searched the reference lists of identified articles for further papers.

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INTRODUCTION

Stroke is the third leading cause of death in developed countries, after heart disease and cancer, and is the most important cause of serious, long-term adult disability and hospitalization. Of the 700,000 strokes that occur annually in the US, approximately 88% are classified as ischemic.¹ Despite extensive evaluation, more than 40% of all ischemic strokes have no clearly identifiable cause and are classified as cryptogenic. The occurrence of cryptogenic strokes is associated with young age, the presence of a superficial infarct, prior transient ischemic attack, and lack of clinically significant weakness in the face and extremities.²

Patent foramen ovale (PFO), a hemodynamically silent interatrial communication present in more than 25% of the US population,³ is the most common cause of systemic right-to-left shunt (RLS). Large-diameter PFOs, which predispose patients to intermittent paradoxical emboli, have been implicated in cryptogenic stroke, platypnea-orthodeoxia syndrome, decompression illness in scuba divers, cerebral fat embolism syndrome and transient global amnesia.^{4,5} Case-control series have reported increased prevalence of PFO in patients with cryptogenic stroke (40–56%) compared with those with no history of stroke (10–18%),^{6–8} and meta-analysis suggests a strong relation between PFO and cryptogenic stroke, especially in people aged younger than 55 years.⁹ Calculations based on these findings suggest that in the US, 98,000–139,000 strokes per year could be attributed to PFO.

The following review summarizes current knowledge regarding PFO as a potential source of cryptogenic stroke. Embryologic origins, diagnostic techniques and treatment options for prevention of paradoxical embolism thought to be related to PFO are discussed. Finally, the emerging and controversial association between PFO and migraine headaches is presented.

WHAT IS A PATENT FORAMEN OVALE?

The foramen ovale is an opening in the interatrial septum resulting from incomplete coverage

of the ostium secundum—an opening within the septum primum—by the septum secundum. The foramen ovale serves as a one-way valve for physiologic right-to-left shunting of oxygenated blood *in utero*. Blood from the placenta enters the right atrium through the inferior vena cava and crosses the foramen ovale into the systemic circulation. Postnatal lung expansion and initiation of the pulmonary circulation reverses the atrial pressure gradient, causing functional closure of the foramen ovale. Fibrosis follows closure and complete fusion of the interatrial septae occurs by 2 years of age in most individuals.¹⁰ Lack of septal fusion results in a PFO, a potential hole that can be opened by reversal of the interatrial pressure gradient or by an intracardiac catheter (Figure 1).

The prevalence of PFO in families is consistent with autosomal dominant inheritance.¹¹ An autopsy study found the frequency of PFO to be 26–40% in normal adult hearts,³ and the mean PFO diameter to be 4.9 mm. Notably, PFO prevalence diminishes with age, from 34% during the first three decades of life, to 25% in individuals aged 30–80 years, and 20% in those aged more than 80 years. Meissner *et al.*¹² corroborated the autopsy study findings in a prospective, population-based study of 581 individuals aged more than 45 years by reporting a PFO prevalence of around 26%.

DETECTION OF PATENT FORAMEN OVALE

PFO can be detected noninvasively by venous injection of agitated saline contrast during transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) or transcranial Doppler imaging. The agitated saline injections are performed at rest and after a calibrated Valsalva maneuver (40 mmHg strain measured by spirometry and sustained for 10 s) or maximal Valsalva maneuver. For detection with TTE or TEE, visualization of an injected saline microbubble in the left atrium or ventricle within three cardiac cycles of right atrial opacification is consistent with the presence of an intracardiac shunt. Notably, introduction of the contrast medium via the inferior vena cava from a femoral vein injection is preferentially directed towards the fossa ovalis and crosses the PFO more readily than an injection from an antecubital vein (100% versus 75% during a Valsalva maneuver; $P < 0.01$), thus allowing for increased detection of RLS.¹³

Shunt detection by transcranial Doppler imaging involves the recording of agitated

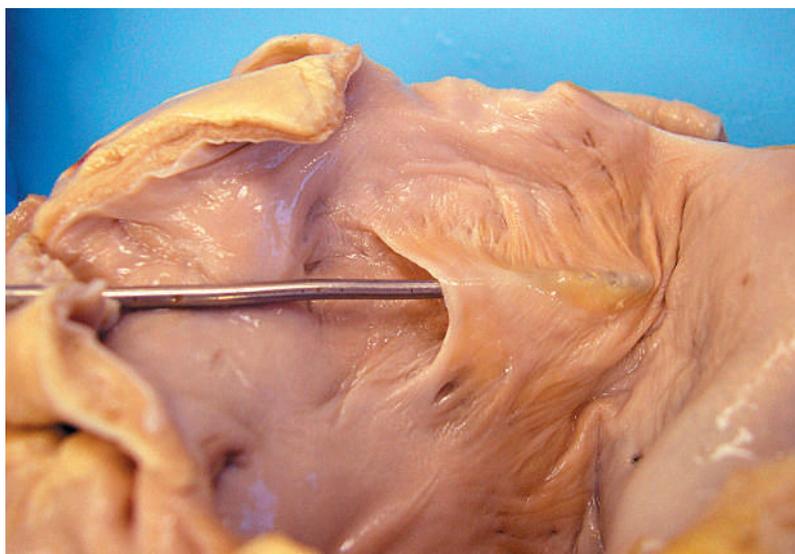


Figure 1 Autopsy specimen illustrating patent foramen ovale, as viewed from the left atrium. The probe is holding up the septum primum. Photograph courtesy of and reproduced with permission from S Mackey, Jesse E Edwards Registry for Cardiovascular Disease, St Paul, MN, USA.

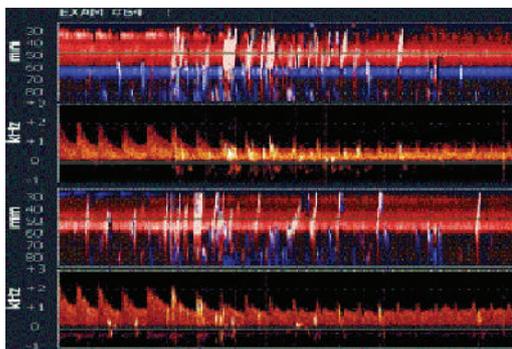


Figure 2 Power motion-mode transcranial Doppler imaging in a patient with a 12 mm diameter patent foramen ovale. This defect was first diagnosed by bilateral power motion-mode transcranial Doppler and subsequently closed with a CardioSEAL[®] device (NMT Medical, Boston, MA). Note the embolic tracks, shown in white, sloping across the red and blue bands of the displays and the presence of some of these microembolic signals in the spectrograms. Reproduced with permission from Spencer Vascular Technologies, Seattle, WA, USA.

saline bubbles mimicking microemboli, passing through the middle cerebral artery during normal respiration or, after a calibrated Valsalva maneuver, as a series of embolic tracks seen on ultrasonography through the temporal bones. By comparison with earlier single-gated technology, power motion-mode transcranial Doppler

imaging employs 33 sample gates to enhance the detection of embolic tracks (Figure 2). Spencer *et al.*¹⁴ reported 98% sensitivity and 94% accuracy when detecting PFO with power motion-mode transcranial imaging, compared with 91% sensitivity and 99% accuracy with TEE. The 'shower' (more than 300 tracks) or 'curtain' (too many tracks to count) patterns of microemboli on transcranial Doppler imaging are consistent with a large RLS and are associated with a higher risk of cryptogenic stroke;¹⁵ however, the presence of microbubbles in the cerebral circulation is not exclusive to an interatrial communication. Any cause of RLS, including ventricular septal defect and pulmonary arteriovenous malformation, can lead to a positive transcranial Doppler reading for an RLS, thus lowering the specificity of this test.¹⁶

TTE, the least sensitive diagnostic method, can fail to detect up to 53% of PFOs.¹⁷ Although power motion-mode transcranial Doppler imaging is a highly sensitive and less invasive method for the detection of RLS, TEE is the accepted 'gold standard' method for PFO documentation. Additionally, PFO diameter can be measured by TEE or by intracardiac echocardiography, which is commonly performed at the time of percutaneous closure for selection of device type and size.

PATENT FORAMEN OVALE AND STROKE

More than 40% of ischemic strokes that occur in people younger than 55 years are cryptogenic.² The prevalence of PFO is higher in patients with cryptogenic stroke than in those with known stroke etiology (45% versus 23%).¹⁷ Notably, this discrepancy is greater in young patients than in older patients, in whom the relative risk of PFO-related stroke decreases as the incidence of hypertension and hyperlipidemia increase.⁷ PFO might have a familial predilection, as reported by Arquizán *et al.*,¹⁸ who found that female siblings of stroke patients with PFO were themselves more likely to have PFO than were siblings of stroke patients without PFO (odds ratio 9.8, $P < 0.01$). Interestingly, this finding was not seen in male siblings of stroke patients with PFO; however, the reason for the difference was not clear.

Multiple potential thromboembolic mechanisms have been proposed to explain the increased risk of recurrent stroke in young patients with PFO. Paradoxical embolism—the systemic passage of thrombi of venous origin

through an interatrial conduit—is thought to be the mechanism of stroke in patients with PFO. Small blood clots and microaggregates could cross the PFO, thereby escaping lysis in the lungs and leading to clinically important sequelae in the brain.¹⁹ The shunting of these particles could occur after a Valsalva maneuver or in relation to a chronic condition causing increased pulmonary artery pressure; however, the clinical diagnosis of paradoxical embolism remains presumptive in the majority of cases. Although the discovery of an *in situ* PFO thrombus is rare, thrombi could form within the PFO tunnel (the 'lurking clot' theory) and enter the systemic circulation during an increase in right atrial pressure.²⁰ Transient atrial arrhythmias are also associated with thrombus formation and higher embolic risks, and could possibly lead to cryptogenic stroke. In addition, patients with cryptogenic stroke and atrial septal abnormalities have increased atrial vulnerability and, therefore, could have a greater potential for paroxysmal atrial fibrillation and thrombus formation.²¹

RISK FACTORS FOR STROKE IN PATIENTS WITH PATENT FORAMEN OVALE

Risk factors for stroke in patients with PFO are presented in Table 1. Increase in PFO diameter has been linked to increased risk of paradoxical embolism. PFO diameter increases with age, from a mean of 3.4 mm in the first decade of life, to 5.8 mm in people aged more than 80 years, suggesting spontaneous late closure of smaller communications.³ Patients with postulated paradoxical embolization appear to have larger PFOs than those without paradoxical embolization, and MRI findings have implicated cerebrovascular emboli as a potential mechanism in stroke patients with a large PFO.²² The presence of spontaneous RLS at rest has also been associated with stroke.²³ In the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), large PFOs—defined as at least 2 mm separation of septa or at least 10 microbubbles in the left atrium—were seen significantly more frequently among patients with cryptogenic stroke than among those with known causes of stroke.²⁴ In addition, the magnitude of RLS through a PFO is a significant risk factor for recurrent cerebrovascular events (odds ratio 14.8 for large PFO [defined as >10 bubbles recorded in the cerebral vessels using single-gated transcranial Doppler and >100 embolic

Table 1 Factors associated with increased risk of cryptogenic stroke in patients with patent foramen ovale.

Risk factor and study	Findings
Large PFO diameter (>2mm)	
Steiner <i>et al.</i> ²²	26% of patients with cryptogenic stroke had large PFO diameter vs 6% with known cause of stroke ($P=0.04$)
Homma <i>et al.</i> ²⁴	2-year recurrent stroke hazard ratio of 0.59 for patients with vs patients without PFO (not significant)
Schuchlenz <i>et al.</i> ²⁸	PFO diameter >4 mm associated with increased risk of ischemic stroke (odds ratio 12, $P=0.0001$)
Large RLS magnitude	
De Castro <i>et al.</i> ²³	Patients with unprovoked RLS had a trend for higher 3-year risk of stroke (12.5% vs 4.3%, $P=0.05$)
Stone <i>et al.</i> ⁶²	Patients with large RLS had more events (31% vs 0, $P=0.03$)
Anzola <i>et al.</i> ²⁵	Relative risk 14.8 for recurrent stroke for patients with large vs small RLS ($P=0.01$)
Coexisting atrial septal aneurysm	
Cabanes <i>et al.</i> ⁸	Odds ratio for cryptogenic stroke 33.3 vs controls ($P=0.0009$)
Overell <i>et al.</i> ⁹ (meta-analysis)	Odds ratio for cryptogenic stroke 17.09 vs stroke of known cause (95% CI 2.19–133.46)
Schuchlenz <i>et al.</i> ²⁸	Odds ratio for stroke 12 vs control ($P=0.001$)
Mas <i>et al.</i> ²⁷	Odds ratio for recurrent stroke 4.17 vs patients without PFO or atrial septal aneurysm ($P=0.007$)
Pelvic DVT	
Cramer <i>et al.</i> ³⁰	Frequency of pelvic DVT increased in cryptogenic stroke patients (9 [20%] of 46, $P<0.025$) and in patients with cryptogenic stroke plus PFO (6 [22%] of 28, $P=0.302$) vs patients with stroke of known origin (2 [4%] of 49)
Clotting factor mutations	
Factor V Leiden	
Pezzini <i>et al.</i> ³¹	11% in PFO patients vs 2.2% in non-PFO patients (not significant)
Prothrombin (G20210A)	
Pezzini <i>et al.</i> ³¹	Odds ratio 10.09 in PFO patients vs non-PFO patients ($P=0.04$)
Lichy <i>et al.</i> ³³	Odds ratio for patients with PFO plus stroke 3.66 vs controls ($P=0.01$)
Either Factor V Leiden or prothrombin G20210A	
Karttunen <i>et al.</i> ³²	Odds ratio for cryptogenic stroke in PFO patients 13.99 vs healthy controls ($P=0.022$)

Abbreviations: DVT, deep vein thrombosis; PFO, patent foramen ovale; RLS, right-to-left shunt.

tracks using power motion-mode transcranial Doppler] versus small PFO, $P=0.01$).^{13,25}

Atrial septal aneurysm is defined as a hypermobile septum primum with at least 10 mm of phasic excursion into either atrium from the septal plane. The prevalence of isolated atrial septal aneurysm in the general population is less than 1% as measured by TTE;²⁶ in patients with cryptogenic stroke, the prevalence is 4–25%.⁷ While atrial septal aneurysm *per se* confers no additional risk for cryptogenic stroke,²⁷ the frequent association of this condition with PFO appears to suggest that it has embolic potential.²⁷ A robust association exists between the combined presence of atrial septal aneurysm and PFO and the primary occurrence of stroke in people younger than

55 years, compared with older people (odds ratio 15.59).⁷ Recurrent stroke, despite aspirin therapy, is also significantly increased in those with both PFO and atrial septal aneurysm, compared with persons with previous stroke without either abnormality or those with atrial septal aneurysm alone ($P=0.007$).²⁷ Persistence of the eustachian valve, a remnant of fetal circulation, can preferentially direct flow through an interatrial communication preventing its spontaneous closure after birth, and indirectly predispose individuals to paradoxical embolism.²⁸

Although they represent the presumed source of embolized clots, less than 10% of all peripheral deep vein thromboses are discovered on diagnostic imaging, a finding that is consistent in

patients with PFO and stroke.²⁹ Investigation for deep vein thrombosis typically involves imaging the femoral and popliteal veins; however, the pelvic veins should also be considered as a potential embolic source. Cramer *et al.*³⁰ found that the incidence of pelvic deep vein thrombosis was significantly higher in patients with cryptogenic stroke (20%) and patients with cryptogenic stroke and PFO (22%) than in patients with stroke of determined origin (4%; $P < 0.025$). Patients with cryptogenic stroke were significantly younger and had fewer risk factors for atherosclerosis than those with stroke of known cause. The prevalence of PFO was 61% in the cryptogenic stroke group and 19% in those with a determined origin of stroke. The finding that most patients with cryptogenic stroke and pelvic deep vein thrombosis also had a PFO supports paradoxical embolism as the stroke mechanism.

Inherited prothrombotic disorders have been linked to an increased risk of venous thromboembolism. Elevated levels of factor VIII, decreased activity of protein C and protein S and antithrombin, and mutations in the factor V Leiden and prothrombin (G20210A mutation) genes have all been associated with ischemic strokes. Pezzini *et al.*³¹ reported that the prothrombin gene G20210A mutation and, to a lesser extent, the factor V Leiden gene mutation were more frequent in PFO patients than non-PFO patients with ischemic stroke. This finding was corroborated by the study of Karttunen *et al.*,³² in which they compared 58 patients with cryptogenic stroke and PFO with 104 matched control patients. They found that patients with PFO in combination with these gene mutations had a significantly increased risk of cryptogenic stroke ($P = 0.022$). By contrast, Lichy *et al.*³³ found only the prothrombin mutation to be more common in patients with stroke and PFO than in stroke patients without PFO and healthy individuals.

TREATMENT OF PATENT FORAMEN OVALE

A lack of randomized trial data means that the optimum management of patients with PFO and cryptogenic stroke is yet to be determined. In the Lausanne Stroke Registry,³⁴ which involved 140 patients with PFO and cryptogenic stroke, 92 patients were treated with a daily regimen of 250 mg aspirin, 37 patients were treated with daily warfarin to an international normalized ratio (INR) of 3.5, and 11 underwent surgical

PFO closure. During a follow-up period of 3 years, annual recurrence rates were 1.9% for ischemic stroke alone and 3.8% for ischemic stroke and transient ischemic attack, which were too low to allow comparisons between therapies. Mas *et al.*²⁷ retrospectively investigated the rate of recurrent stroke despite treatment with 250–500 mg aspirin or warfarin daily (target INR 2–3) during a 23-month follow-up. In 132 patients with cryptogenic stroke—69 of whom had an isolated PFO, 25 an isolated atrial septal aneurysm and 38 of whom had both—there was a 1.2% annual rate of recurrent ischemic stroke alone, and a 3.4% annual rate of ischemic stroke and transient ischemic attack. In the subgroup of patients with PFO and atrial septal aneurysm, the annual rates were 4.4% and 11.7%, respectively. The 4-year cumulative risk for recurrent stroke in this subgroup was 15.2%. In the PICSS trial²⁴ there was no difference in mortality or recurrent stroke rates at 2 years between patients who received 325 mg aspirin daily or warfarin therapy (target INR 1.4–2.8). In a secondary analysis of this trial, patients with PFO aged 65 years or older had an increased risk of death or recurrent ischemic stroke compared with age-matched patients without PFO (hazard ratio 2.92, $P = 0.01$).³⁵ A raised risk of adverse effects was not seen in PFO patients aged younger than 65 years.

Surgical closure of PFO, a procedure requiring general anesthesia and cardiopulmonary bypass, has been used to prevent recurrent cryptogenic stroke. The results of selected surgical PFO closure studies are presented in Table 2. Major perioperative complications of surgical PFO closure include postpericardiotomy syndrome (2.3%), tamponade (1.9%), exploratory reoperation (1.4%), and ventricular fibrillation (0.5%).^{36–38}

Transcatheter closure of PFO has been developed as a minimally invasive alternative to surgery. The procedure, which involves percutaneous implantation of a device to occlude the interatrial septum, allows patients to be discharged from hospital within 24 h. Although multiple PFO closure devices have been developed, only the CardioSEAL® (NMT Medical, Boston, MA) and Amplatzer® (AGA Medical, Golden Valley, MN) devices are approved by the FDA.³⁹ A 0–6% rate of recurrent stroke or transient ischemic attack is reported after transcatheter PFO closure, as shown in Table 3.^{40–48} High rates of recurrent cerebrovascular events

Table 2 Results of selected studies of surgical patent foramen ovale closure to treat recurrent stroke.

Study	Number of patients (% female)	Mean follow-up in months (range)	Incidence (%) of cerebrovascular event recurrence and time after closure	Number (%) of patients with residual shunt
Devuyt <i>et al.</i> ³⁸	30 (67)	23 (0–38)	0	3 (10)
Homma <i>et al.</i> ³⁶	28 (39)	19 (1–52)	19.5 at 13 months	NA
Dearani <i>et al.</i> ³⁷	91 (36)	23 (NA)	7.5 at 1 year, 16.5 at 4 years	NA

Abbreviations: NA, not available.

Table 3 Reports of recurrent stroke in patients following transcatheter patent foramen ovale closure.

Study	Number of patients (% female)	Device used (% of patients)	Mean follow-up in years (range)	Number of placement failures (%)	Proportion with stroke recurrence after closure (%)	Number with residual shunt (%)
Hung <i>et al.</i> ⁴⁰	63 (43)	Clamshell (44), Sideris buttoned (35), CardioSEAL ^{®a} (21)	2.6 (0.1–8.2)	0	6	9 (14)
Wahl <i>et al.</i> ⁴¹	152 (47)	Amplatzer ^{®b} (36), PFO-STAR [™] (29), Sideris buttoned (21), CardioSEAL ^{®a} or STARFlex ^{®a} (7), Angel Wings ^{®c} (7)	1.7 (0.1–6.5)	2 (1)	4.9	32 (21)
Bruch <i>et al.</i> ⁴²	66 (NA)	Amplatzer ^{®b} (93), PFO-Star [™] (3), CardioSEAL ^{®a} or STARFlex ^{®a} (3)	NA (0.1–3.6)	0	0	2 of 66 (3) at 3 months
Onorato <i>et al.</i> ⁴³	256 (41)	Amplatzer ^{®b} (97), HELEX ^{®d} (2), PFO-STAR [™] (2)	1.6 (0.1–2.8)	0	0	NA (2)
Hong <i>et al.</i> ⁴⁴	50 (44)	Amplatzer ^{®b} (100)	1.4 (1 day to 2.3 years)	0	0	3 (6)
Giardini <i>et al.</i> ⁴⁵	72 (44)	Amplatzer ^{®b} (58), STARFlex ^{®a} (42)	1.7 (0.1–4.9)	2 (2.8)	2.4	5 of 65 (8) at 6 months
De Ridder <i>et al.</i> ⁴⁶	32 (69)	Amplatzer ^{®b} (100)	1.3 (0.03–5.3)	2 (6)	0	2 (7)
Chatterjee <i>et al.</i> ⁴⁷	55 (38)	Amplatzer ^{®b} (100)	1.6 (0.3–2.7)	0	0	2 (4)
Windecker <i>et al.</i> ⁶³	150 (47)	Amplatzer ^{®b} PFO occluder (36) PFO-STAR [™] (28) Sideris buttoned (18) Angel Wings ^{®c} (6) Amplatzer ^{®b} ASD occluder (6) CardioSEAL ^{®a} (5)	2.3 (0.6–4.0)	2 (1)	1	26 (17)
Schuchlenz <i>et al.</i> ⁴⁸	167 (46)	Amplatzer ^{®b} (54), CardioSEAL ^{®a} or STARFlex ^{®a} (42), Rashkind ^{®e} (4)	2.8	3 (2)	0.6	NA

^aNMT Medical, Boston, MA; ^bAGA Medical, Golden Valley, MN; ^cev3 Inc, Plymouth, MN; ^dWL Gore & Associates, Newark, DE; ^eWL Rashkind, Philadelphia, PA, USA. Abbreviations: NA, not available; PFO, patent foramen ovale.

were seen with the use of earlier closure devices, such as the Rashkind[®] hook device (WJ Rashkind, Philadelphia, PA),^{40,41,48} and in patients with residual RLS.⁴¹ Early devices were also less effective in achieving total PFO closure than the currently available devices.⁴¹ The presence of a thrombophilic disorder with PFO did not affect the rate of recurrent cerebrovascular events after closure.⁴⁵ Notably, reported complications following PFO closure are infrequent and are associated with low

morbidity and mortality. Long-term consequences of PFO closure are unknown. In a study of 276 patients with stroke and PFO closure, Hung *et al.*⁴⁰ found that adverse events included brief atrial fibrillation (0.8%), device dislodgement (0.4%), device arm fracture (3.6%) and surgical explantation (0.8%). Migraine headaches that occur after percutaneous closure of atrial septal defects have not been reported after transcatheter PFO closure.⁴⁹ In 1,000 patients who underwent

Table 4 The major studies of migraine relief following transcatheter closure of patent foramen ovale.

Study	Number of patients (% female)	Mean age in years (SD)	Number (%) of patients with migraine with aura	Mean follow-up	Resolution	Reduced severity or frequency	Unchanged
Wilmshurst <i>et al.</i> ¹⁸	21 (48)	NA	16 (76)	1.5–32.0 months ^a	48% (44% with aura, 60% without aura)	38% (50% with aura, 0% without aura)	14% (6% with aura, 40% without aura)
Morandi <i>et al.</i> ⁶⁴	17 (71)	48 (15)	9 (53)	6 months	29%	59%	12%
Schwerzmann <i>et al.</i> ⁶⁵	48 (65)	49 (11) migraine with aura, 42 (12) migraine without aura	37 (77)	1.7 years	NA	54% with aura, 62% without aura	3 with aura and large residual shunt
Azarbal <i>et al.</i> ⁶⁶	37 (66)	NA	20 (54)	12 months	75% with aura, 40% without aura	5% with aura, 40% without aura	NA
Reisman <i>et al.</i> ⁶¹	57 (67)	47 (12)	39 (68)	37 weeks	56% (54% with aura, 62% without aura)	14% (14% with aura, 15% without aura)	30% (32% with aura, 23% without aura)

^aRange. Abbreviation: NA, not available.

PFO closure, deployment of the Amplatzer® device resulted in lower rates of postprocedure thrombi than use of the CardioSEAL®, STARFlex® (NMT Medical, Boston, MA) and PFO-Star™ (Cardia Inc, Burnsville, MN) devices (0, 7.1%, 5.7%, and 6.6%, respectively; $P < 0.05$).⁵⁰ Thrombus formation was not associated with clinical events, for example stroke, and has been shown to be reduced by aspirin and clopidogrel use until the device is endothelialized, which generally takes 2–4 months.

Several nonrandomized studies have attempted to compare surgical or transcatheter PFO closure with medical PFO treatment. Bogousslavsky *et al.*³⁴ reported that stroke recurrence was not related to the method of treatment (i.e. surgical closure versus medication); however, Khairy *et al.*⁵¹ reviewed data from 10 PFO closure studies and 6 medical therapy studies and reported a 1-year recurrence rate of 3.8–12.0% for medical therapy compared with 0–4.9% for surgical or transcatheter closure. Patients who underwent PFO closure were more likely to have multiple cerebrovascular events, but this finding could be related to selection bias. Schuchlenz *et al.*⁴⁸ reported that the rate of recurrent cerebrovascular events in the patients treated with closure was 0.6% per year, significantly lower than that in patients receiving warfarin (5.6%) and aspirin (13%). Two randomized

trials comparing medical therapy using aspirin, warfarin, or both, with closure are in progress: the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) study, sponsored by AGA, and Closure I, sponsored by NMT Medical. Despite the lack of randomized trials, the evidence indicates that transcatheter PFO closure is associated with better long-term outcome than medical treatment alone.

MIGRAINE AND PATENT FORAMEN OVALE

Migraine headache, categorized as either classic (with aura) or common (without aura), is a paroxysmal, often debilitating, condition affecting about 13% of the US adult population.⁵² Patients who have migraines with aura are more likely than those who have migraines without aura or those without migraines altogether to have a PFO.⁵³ Schwerzmann *et al.*⁵⁴ reported that PFO was more frequently seen among people who had migraine with aura than among controls matched for age and sex (47% versus 17%). A large RLS was seen in 57% of patients with migraines and 16% of control patients. The odds ratio of having migraine in the presence of PFO with a moderate or large RLS was 7.78 (95% CI 2.53–29.3, $P < 0.001$), suggesting that interatrial communication might be associated with migraine pathogenesis.

Evidence indicates an association between migraine, stroke and PFO. Although the overall risk of stroke in patients with migraine headaches is low,⁵⁵ cryptogenic stroke patients with PFO are twice as likely to have a history of migraine headache as those without PFO (27% versus 14%).⁵⁶ Patients younger than 45 years with migraine and stroke had a higher prevalence of posterior circulation infarcts than stroke patients without migraine, matched for age and sex (55% versus 34%, $P < 0.01$).⁵⁷ Patients who had classic migraine had an increased prevalence of subclinical posterior circulation infarcts compared with those with common migraine (8.1% versus 2.2%, $P = 0.03$).⁵⁸ The odds ratio for risk of ischemic stroke among patients with migraine in the Physicians' Health Study was 2.00 (95% CI 1.10–3.64).⁵⁹ The relative risk for stroke is 2.88 (95% CI 1.89–4.39) for migraine with aura and 1.56 (95% CI 1.03–2.36) for migraine without aura.⁶⁰ These data have led to the theory that interatrial transit of microemboli or vasoactive compounds through the PFO evades pulmonary filtration and results in cerebral vasoreactivity and migraine symptoms, ischemic stroke, or both.⁵⁴ Several small studies have suggested that PFO closure in patients with cryptogenic stroke or decompression illness could reduce migraine symptoms. The findings of these trials are listed in Table 4. Unfortunately, these studies were limited by nonrandomized design, small sample size and lack of a control group. The results must, therefore, be interpreted cautiously. Nevertheless, the migraine resolution rate (i.e. complete cessation of headache) following PFO closure was 29–60%, and 14–59% of patients saw improvement in severity or frequency of headaches. Our group found a net reduction in migraine episodes per month of 80% (6.8 ± 9.6 before closure versus 1.4 ± 3.4 after closure, $P < 0.001$).⁶¹ Migraine relief was independent of closure status at 1-year follow-up.

The data presented here point to the need for large randomized trials designed to assess the efficacy of PFO closure in reducing the incidence of migraine headaches. An example of such a trial is the Migraine Intervention with STARFlex® Technology (MIST) trial, sponsored by NMT Medical, a randomized UK-based trial designed to determine the effect of PFO closure on migraine frequency. A similar study is about to launch in the US.

CONCLUSIONS

PFO is a risk factor for cryptogenic stroke, independent of traditional risk factors, particularly in people younger than 55 years. The continued risk of recurrent neurologic events despite medical therapy warrants consideration of PFO closure as a treatment option. Prospective multicenter trials are needed to determine whether PFO closure can reduce the disability associated with recurrent stroke or migraine headaches.

KEY POINTS

- More than 40% of all ischemic strokes have no identifiable cause and are classified as cryptogenic
- Paradoxical emboli, through a right-to-left shunt, have been implicated as a cause of cryptogenic stroke
- Patent foramen ovale, the most common cause of a right-to-left shunt, can be detected noninvasively by agitated saline bubble study during echocardiography or transcranial Doppler imaging
- Transcatheter closure of patent foramen ovale has been developed as a minimally invasive alternative for prevention of stroke caused by paradoxical emboli
- Transcatheter patent foramen ovale closure has been associated with a reduction or cessation of complex migraine headaches with aura in nonrandomized studies
- Randomized trials are underway to evaluate the efficacy of transcatheter patent foramen ovale closure on prevention of recurrent ischemic stroke and complex migraine

References

- 1 American Heart Association (online 11 January 2006) Heart Disease and Stroke Statistics—2006 Update [http://www.americanheart.org/presenter.jhtml?identifier=1928] (accessed 20 April 2006)
- 2 Sacco RL *et al.* (1989) Infarcts of undetermined cause: the NINCDS Stroke Data Bank. *Ann Neurol* **25**: 382–390
- 3 Hagen PT *et al.* (1984) Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* **59**: 17–20
- 4 Meier B and Lock JE (2003) Contemporary management of patent foramen ovale. *Circulation* **107**: 5–9
- 5 Klötzsch C *et al.* (1996) An increased frequency of patent foramen ovale in patients with transient global amnesia: analysis of 53 consecutive patients. *Arch Neurol* **53**: 504–508
- 6 Webster MW *et al.* (1988) Patent foramen ovale in young stroke patients. *Lancet* **2**: 11–12
- 7 Lechat P *et al.* (1988) Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* **318**: 1148–1152

- 8 Cabanes L *et al.* (1993) Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. *Stroke* **24**: 1865–1873
- 9 Overell JR *et al.* (2000) Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* **55**: 1172–1179
- 10 Kerut EK *et al.* (2001) Patent foramen ovale: a review of associated conditions and the impact of physiological size. *J Am Coll Cardiol* **38**: 613–623
- 11 Wilmschurst PT *et al.* (2004) Inheritance of persistent foramen ovale and atrial septal defects and the relation to familial migraine with aura. *Heart* **90**: 1315–1320
- 12 Meissner I *et al.* (1999) Prevalence of potential risk factors for stroke assessed by transesophageal echocardiography and carotid ultrasonography: the SPARC study. *Stroke Prevention: Assessment of Risk in a Community. Mayo Clin Proc* **74**: 862–869
- 13 Hamann GF *et al.* (1998) Femoral injection of echo contrast medium may increase the sensitivity of testing for a patent foramen ovale. *Neurology* **50**: 1423–1428
- 14 Spencer MP *et al.* (2004) Power m-mode transcranial Doppler for diagnosis of patent foramen ovale and assessing transcatheter closure. *J Neuroimaging* **14**: 342–349
- 15 Serena J *et al.* (1998) The need to quantify right-to-left shunt in acute ischemic stroke: a case-control study. *Stroke* **29**: 1322–1328
- 16 Jauss M *et al.* (2000) Detection of right-to-left shunt with ultrasound contrast agent and transcranial Doppler sonography. *Cerebrovasc Dis* **10**: 490–496
- 17 Di Tullio M *et al.* (1993) Comparison of diagnostic techniques for the detection of a patent foramen ovale in stroke patients. *Stroke* **24**: 1020–1024
- 18 Arquizan C *et al.* (2001) Is patent foramen ovale a family trait? A transcranial Doppler sonographic study. *Stroke* **32**: 1563–1566
- 19 Wilmschurst PT *et al.* (2000) Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. *Lancet* **356**: 1648–1651
- 20 Falk V *et al.* (1997) Trapped thrombus in a patent foramen ovale. *Thorac Cardiovasc Surg* **45**: 90–92
- 21 Berthet K *et al.* (2000) Significant association of atrial vulnerability with atrial septal abnormalities in young patients with ischemic stroke of unknown cause. *Stroke* **31**: 398–403
- 22 Steiner MM *et al.* (1998) Patent foramen ovale size and embolic brain imaging findings among patients with ischemic stroke. *Stroke* **29**: 944–948
- 23 De Castro S *et al.* (2000) Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke* **31**: 2407–2413
- 24 Homma S *et al.* (2002) Effect of medical treatment in stroke patients with patent foramen ovale: Patent Foramen Ovale in Cryptogenic Stroke Study. *Circulation* **105**: 2625–2631
- 25 Anzola GP *et al.* (2003) Transcranial Doppler and risk of recurrence in patients with stroke and patent foramen ovale. *Eur J Neurol* **10**: 129–135
- 26 Hanley PC *et al.* (1985) Diagnosis and classification of atrial septal aneurysm by two-dimensional echocardiography: report of 80 consecutive cases. *J Am Coll Cardiol* **6**: 1370–1382
- 27 Mas JL *et al.* (2001) Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med* **345**: 1740–1746
- 28 Schuchlenz H *et al.* (2004) Persisting eustachian valve in adults: relation to patent foramen ovale and cerebrovascular events. *J Am Soc Echocardiogr* **17**: 231–233
- 29 Ranoux D *et al.* (1993) Patent foramen ovale: is stroke due to paradoxical embolism? *Stroke* **24**: 31–34
- 30 Cramer SC *et al.* (2004) Increased pelvic vein thrombi in cryptogenic stroke: results of the Paradoxical Emboli From Large Veins in Ischemic Stroke (PELVIS) Study. *Stroke* **35**: 46–50
- 31 Pezzini A *et al.* (2003) Inherited thrombophilic disorders in young adults with ischemic stroke and patent foramen ovale. *Stroke* **34**: 28–33
- 32 Karttunen V *et al.* (2003) Factor V Leiden and prothrombin gene mutation may predispose to paradoxical embolism in subjects with patent foramen ovale. *Blood Coagul Fibrinolysis* **14**: 261–268
- 33 Lichy C *et al.* (2003) Prothrombin G20210A mutation, but not factor V Leiden, is a risk factor in patients with persistent foramen ovale and otherwise unexplained cerebral ischemia. *Cerebrovasc Dis* **16**: 83–87
- 34 Bogousslavsky J *et al.* (1996) Stroke recurrence in patients with patent foramen ovale: the Lausanne Study. Lausanne Stroke with Paradoxical Embolism Study Group. *Neurology* **4**: 1301–1305
- 35 Homma S *et al.* (2004) Age as a determinant of adverse events in medically treated cryptogenic stroke patients with patent foramen ovale. *Stroke* **35**: 2145–2149
- 36 Homma S *et al.* (1997) Surgical closure of patent foramen ovale in cryptogenic stroke patients. *Stroke* **28**: 2376–2381
- 37 Dearani JA *et al.* (1999) Surgical patent foramen ovale closure for prevention of paradoxical embolism-related cerebrovascular ischemic events. *Circulation* **100 (Suppl)**: II171–II175
- 38 Devuyst G *et al.* (1996) Prognosis after stroke followed by surgical closure of patent foramen ovale: a prospective follow-up study with brain MRI and simultaneous transesophageal and transcranial Doppler ultrasound. *Neurology* **47**: 1162–1166
- 39 Landzberg MJ and Khairy P (2004) Indications for the closure of patent foramen ovale. *Heart* **90**: 219–224
- 40 Hung J *et al.* (2000) Closure of patent foramen ovale for paradoxical emboli: intermediate-term risk of recurrent neurological events following transcatheter device placement. *J Am Coll Cardiol* **35**: 1311–1316
- 41 Wahl A *et al.* (2001) Prognosis after percutaneous closure of patent foramen ovale for paradoxical embolism. *Neurology* **57**: 1330–1332
- 42 Bruch L *et al.* (2002) Transcatheter closure of interatrial communications for secondary prevention of paradoxical embolism: single center experience. *Circulation* **105**: 2845–2848
- 43 Onorato E *et al.* (2003) Patent foramen ovale with paradoxical embolism: mid-term results of transcatheter closure in 256 patients. *J Interv Cardiol* **16**: 43–50
- 44 Hong TE *et al.* (2003) Transcatheter closure of patent foramen ovale associated with paradoxical embolism using the Amplatzer® PFO occluder: initial and intermediate-term results of the US multicenter clinical trial. *Catheter Cardiovasc Interv* **60**: 524–528
- 45 Giardini A *et al.* (2004) Comparison of results of percutaneous closure of patent foramen ovale for paradoxical embolism in patients with versus without thrombophilia. *Am J Cardiol* **94**: 1012–1016
- 46 De Ridder S *et al.* (2005) Percutaneous transcatheter closure of atrial septal defects: initial single-center experience and follow-up results. Initial experience with three-dimensional echocardiography. *Acta Cardiol* **60**: 171–178
- 47 Chatterjee T *et al.* (2005) Interventional closure with Amplatzer® PFO occluder of patent foramen ovale in patients with paradoxical cerebral embolism. *J Interv Cardiol* **18**: 173–179

- 48 Schuchlenz HW *et al.* (2005) Secondary prevention after cryptogenic cerebrovascular events in patients with patent foramen ovale. *Int J Cardiol* **101**: 77–82
- 49 Sharifi M *et al.* (2005) Intense migraines secondary to percutaneous closure of atrial septal defects. *J Interv Cardiol* **18**: 181–183
- 50 Krumdsorf U *et al.* (2004) Incidence and clinical course of thrombus formation on atrial septal defect and patent foramen ovale closure devices in 1,000 consecutive patients. *J Am Coll Cardiol* **43**: 302–309
- 51 Khairy P *et al.* (2003) Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med* **139**: 753–760
- 52 Lipton RB *et al.* (2002) Migraine in the United States: epidemiology and patterns of health care use. *Neurology* **58**: 885–894
- 53 Del Sette M *et al.* (1998) Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. *Cerebrovasc Dis* **8**: 327–330
- 54 Schwerzmann M *et al.* (2005) Prevalence and size of directly detected patent foramen ovale in migraine with aura. *Neurology* **65**: 1415–1418
- 55 Kurth T *et al.* (2005) Migraine, headache, and the risk of stroke in women: a prospective study. *Neurology* **64**: 1020–1026
- 56 Lamy C *et al.* (2002) Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. Atrial Septal Aneurysm. *Stroke* **33**: 706–711
- 57 Milhaud D *et al.* (2001) Ischemic stroke and active migraine. *Neurology* **57**: 1805–1811
- 58 Kruit MC *et al.* (2004) Migraine as a risk factor for subclinical brain lesions. *JAMA* **291**: 427–434
- 59 Buring JE *et al.* (1995) Migraine and subsequent risk of stroke in the Physicians' Health Study. *Arch Neurol* **52**: 129–134
- 60 Etminan M *et al.* (2005) Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *BMJ* **330**: 63–64
- 61 Reisman M *et al.* (2005) Migraine headache relief after transcatheter closure of patent foramen ovale. *J Am Coll Cardiol* **45**: 493–495
- 62 Stone DA *et al.* (1996) Patent foramen ovale: association between the degree of shunt by contrast transesophageal echocardiography and the risk of future ischemic neurologic events. *Am Heart J* **131**: 158–161
- 63 Windecker S *et al.* (2004) Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. *J Am Coll Cardiol* **44**: 750–758
- 64 Morandi E *et al.* (2003) Transcatheter closure of patent foramen ovale: a new migraine treatment? *J Interv Cardiol* **16**: 39–42
- 65 Schwerzmann M *et al.* (2004) Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. *Neurology* **62**: 1399–1401
- 66 Azarbal B *et al.* (2005) Association of interatrial shunts and migraine headaches: impact of transcatheter closure. *J Am Coll Cardiol* **45**: 489–492

Competing interests

The authors declared they have no competing interests.