Editorial Guest

Cryptogenic stroke and PFO diagnosis

JM Juliard[1], P Aubry[1], M Mazighi [2], E Brochet[1], P Charlier[1], D Enguerrand[3], C Berroeta[3], L Lepage[1], A Vahanian[1], P Amarenco[2]

[1]Department of Cardiology, [2]Department of Neurology and Stroke Center, [3]Department of Anaesthesiology, Hôpital Bichat, Paris, France

There is a strong causal relationship between Patent Foramen Ovale (PFO) and the occurrence of a first cryptogenic stroke in young patients under 60 years of age. This relationship is stronger when PFO is associated with atrial septal aneurysm (ASA). Transthoracic echocardiography with contrast testing can reveal evidence of PFO, which should be confirmed using transesophageal echocardiography. Before searching for PFO the neurologic team must perform a thorough neurologic evaluation to ascertain that the stroke has no other known cause. The implications of PFO and ASA are not clearly understood but many hypotheses have been put forward. These comprise local formation of thrombi, paradoxical embolism, increased atrial vulnerability, etc. Indication of PFO closure must be discussed in close collaboration with the neurologic team. Even if percutaneous closure is a safe procedure, the risk of recurrent neurologic events after PFO closure exists. Retrospective, non-randomized studies have shown that the risk of recurrent neurologic events is lower in patients who underwent PFO closure compared to those who were medically treated. There are numerous ongoing randomized trials, but their completion appears to be far off, due to patient preference for PFO closure as opposed to long-term anticoagulant therapy. In the future, our challenge is to make percutaneous closure safer and more efficient, this may be achieved through technical advances with bio-absorbable devices or device-free, radiofrequency closure. A randomized study in this setting is the only way forward, however, it is only viable if we are able to provide timely results. A large multi-center registry can also generate reliable data regarding procedural complications, residual leak and recurrent stroke rates.

Patent Foramen Ovale (PFO) is a vestige of the fetal circulation and results from failure of the primum and secundum septa to fuse postnatally. The autopsy-derived prevalence of probe-patent PFO is about 27% with decreasing prevalence with age[1]. These figures are consistent with those obtained in the SPARC prevention study with a prevalence of 25.6% using both transesophageal echocardiography (TEE) and transcranial Doppler examination approaches[2].

Stroke is a leading cause of death and long-term disability worldwide. On the whole, 20% of strokes are hemorrhagic and the remainder are ischemic, and most ischemic strokes occur in patients older than 65 years of age in tandem with the development of atherosclerosis. However, as many as half the patients referred to tertiary care centers are younger than 65, and up to 12% are younger than 45 years of age[3].

In young patients there is a strong causal relationship between PFO and the occurrence of a first cryptogenic stroke in young patients under 60 years of age. This relationship is stronger when PFO is associated with atrial septal aneurysm (ASA). Transthoracic echocardiography with contrast testing can reveal evidence of PFO, which

Correspondence: Jean-Michel Juliard, MD, Département de Cardiologie, Hôpital Bichat, 46 rue Henri Huchard 75877 PARIS Cedex 18, France. Tel: 33 1 40 25 66 01, Fax: 33 1 40 25 88 65, E-mail: jean-michel.juliard@bch.aphp.fr

should be confirmed using transesophageal echocardiography. Before searching for PFO the neurologic team must perform a thorough neurologic evaluation to ascertain that the stroke has no other known cause. The implications of PFO and ASA are not clearly understood but many hypotheses have been put forward. These comprise local formation of thrombi, paradoxical embolism, increased atrial vulnerability, etc. Indication of PFO closure must be discussed in close collaboration with the neurologic team. Even if percutaneous closure is a safe procedure, the risk of recurrent neurologic events after PFO closure exists. Retrospective, non-randomized studies have shown that the risk of recurrent neurologic events is lower in patients who underwent PFO closure compared to those who were medically treated. There are numerous ongoing randomized trials, but their completion appears to be far off, due to patient preference for PFO closure as opposed to long-term anticoagulant therapy. In the future, our challenge is to make percutaneous closure safer and more efficient, this may be achieved through technical advances with bio-absorbable devices or device-free, radiofrequency closure. A randomized study in this setting is the only way forward, however, it is only viable if we are able to provide timely results. A large multi-center registry can also generate reliable data regarding procedural complications, residual leak and recurrent stroke rates.

Patent Foramen Ovale (PFO) is a vestige of the fetal circulation and results from failure of the primum and secundum septa to fuse postnatally. The autopsy-derived prevalence of probe-patent PFO is about 27% with decreasing prevalence with age[1]. These figures are consistent with those obtained in the SPARC prevention study with a prevalence of 25.6% using both transesophageal echocardiography (TEE) and transcranial Doppler examination approaches[2].

Stroke is a leading cause of death and long-term disability worldwide. On the whole, 20% of strokes are hemorrhagic and the remainder are ischemic, and most ischemic strokes occur in patients older than 65 years of age in tandem with the development of atherosclerosis. However, as many as half the patients referred to tertiary care centers are younger than 65, and up to 12% are younger than 45 years of age[3].

In young patients there is a strong causal relationship between PFO and the occurrence of a first cryptogenic stroke[4]. Numerous case-control studies have shown that the prevalence of PFO in young patients (<55 years) presenting with a stroke of unknown cause is as high as 60%. The prevalence of PFO in cryptogenic stroke patients is five times higher than in non-stroke patients[5]. This relationship is even stronger when the PFO is associated with an atrial septal aneurysm (ASA, defined as an interatrial septum of abnormal mobility with protrusion of the septum into the left or right atrium of at least 10 mm beyond the baseline[6].

Stroke of unknown cause: how to confirm the diagnosis?

Before considering the role of the PFO in a young patient presenting with a stroke, a thorough examination by the neurologic team is required to rule out all other possible causes. Brain infarction is confirmed using cerebral computed tomography or magnetic resonance imaging. Magnetic resonance angiography is mandatory for excluding cervical artery dissection. Various methods are required to identify other cardiovascular thromboembolic risks, such as ultrasonography and magnetic resonance angiography for atherosclerotic plaque in the ascending aorta or extracranial arteries; blood coagulation tests including protein C and S, antithrombin III, fibrinogen, antiphospholipid antibodies and APC resistance to identify those in a prothrombotic state; and continuous monitoring at the acute stage and subsequent 24-h ECG-Holter monitoring for those suffering from paroxysmal atrial fibrillation.

When all these potential causes have been excluded, PFO must be considered as a potential mechanism of the neurologic event.

Relationship between PFO and stroke of unknown cause

The exact role of the PFO is not clear even in a young patient with a stroke of unknown cause. Unless there is a clear identification of a thrombus formation inside the tunnel (paradoxical embolism) of the PFO, it can be viewed either as an innocent bystander or as the key determinant of the stroke.

In these young patients, PFO has no hemodynamic consequences, and numerous hypothesis have been put forward to explain its potential implication: Local formation of thrombi, inside the tunnel, increased atrial vulnerability and the risk of subsequent atrial fibrillation, however, in current practice we have not observed any increase in the incidence of symptomatic atrial fibrillation in these patients[7], paradoxical embolism, considering that pelvic deep vein thrombosis is increased in the cryptogenic population as compared to controls[8].

In combination with PFO, ASA could act as a facilitator for embolism, by increasing the PFO diameter or by promoting the flow from the inferior vena cava especially when ASA is associated with a Chiari network (remnant of the right valve of the sinus venosus) or the presence of an Eustachian valve, commonly found in these patients. A study-using TEE with contrast testing suggested the importance of Chiari network (prevalence: 2% in 1,436 consecutive adult patients) as, 83% were affected by both, PFO and Chiari network[9]. The Chiari network is more common in cryptogenic stroke patients than in patients evaluated for other indications (4.6% vs 0.5%), and it may facilitate paradoxical embolism.

Risk of recurrent neurological events in young patients presenting with a PFO

After a first brain infarction or transient ischemic attack (TIA), the therapeutic goal is to prevent recurrent neurologic events in such young patients. Ten years ago, Mas et al. already underlined that the risk of recurrent neurologic event was 4.4%/yr in 38 pts with PFO and ASA[10]. A prospective study of 598 young patients (<55 years) presenting with cryptogenic stroke showed that 36% had PFO, 1.7% ASA, and 8.5% had both abnormalities[11]. Despite aspirin therapy in all patients, those with both PFO and ASA are at higher risk for recurrent stroke (4% per year) compared with those with PFO alone or no septum abnormality (1% per year), thus preventive strategies should be considered in these patients. However, in this study the confidence interval was very large and most events occurred during the 4th year of follow-up, with no clear explanation. Therefore, two therapeutic options are offered, which are either long-term anticoagulant therapy with an intrinsic hemorrhagic risk close to 1% per year or percutaneous closure and antiplatelet agents.

However, the benefit of anticoagulant therapy has never been established. The Warfarin-Aspirin Recurrent Stroke Study (WARSS) was a prospective trial of 2,206 patients aged from 30 to 85 years with prior stroke[12]. Patients were randomized between aspirin (325 mg per day) and warfarin (target INR: 1.4 to 2.8). After two years, there were no significant differences between aspirin and warfarin for recurrent stroke or death, with the same pattern in patients with cryptogenic stroke. The PFO in Cryptogenic Stroke Study (PICSS) study was an ancillary study of the WARSS, considering patients who had had a thorough echocardiographic evaluation[13]. At two years, this study concluded that large PFO or ASA in stroke patients did not increase the chance of recurrent neurological events. The results of this study must be interpreted with caution since the two studies are not comparable: in the PICSS study patients were older, the mean INR was not optimal (2.04), and death, which is not a common criteria in young patients with a first neurological event was included as endpoint. However, in this study, patients with PFO and stroke of unknown cause (n = 98) had fewer primary endpoints on warfarin (9.5%) than on aspirin (17.9%), a difference that was not significant (p=0.28).

Clinical benefit of percutaneous PFO closure

In 2007, we have no evidence of the efficacy of

PFO closure for reducing the risk of recurrent neurological events after a first cryptogenic stroke. No prospective randomized trials comparing PFO closure and medical therapy have been reported so far, even in high-risk patients. However, the feasibility and the safety of this procedure have currently been reported in numerous and large series and the reliability of the new device's implantation must now be compared to medical treatment, in particular long-term anticoagulation[14-17]. With the new devices, invasive approaches are becoming easier, more reliable and safer, which explains the difficulties in concluding the ongoing randomized trials (RESPECT, CARDIA STAR, CLOSURE I trials), since most of the patients preferred PFO closure and refused long-term anticoagulant therapy[18]. Most of the studies are retrospective. In a large but non-randomized study comprising 150 patients undergoing PFO closure and 158 treated medically, PFO closure was compared to medical treatment[19]. At four years of follow-up, the rate of recurrent stroke or TIA was lower in the interventional group than those treated medically, although the difference was not statistically significant, 7.8% vs 22.2% (p=0.08). With respect to the additional presence of ASA, no difference was observed in recurrence rates between the medically treated and PFO closure groups. Patients with more than one cerebrovascular event at baseline and those with complete occlusion of PFO were at lower risk of recurrent stroke or TIA after PFO closure compared with medically treated patients (7.3% vs 33.2%, p = 0.01).

Efficacy of percutaneous closure seems similar in 141 PFO-patients with or without ASA[20]. In patients with PFO and ASA, 95% were free of recurrent TIA, stroke and peripheral embolism at four years. Results were similar (94%) to patients who were treated in the same way for PFO alone. The only predictor for recurrence was a residual right-to-left shunt after the intervention. In a large series of 403 patients, residual shunt was present in 10.8%, at 6-month follow-up[21].

Percutaneous closure was successfully achieved in a very carefully selected cohort of 40 consecutive patients under 60 years, with recent cryptogenic stroke and PFO plus ASA[22]. Neurological examination was performed every three months by a neurologist in order to check for possible recurrent stroke. On midterm follow-up (17 months, and at least 12 months for each patient) in this high-risk patient group, we observed no recurrent neurological events (neither stroke nor TIA). Obviously, the number of patients was too small and the duration of the follow-up was too short to draw any firm conclusion regarding the benefit of this interventional strategy. However, the safety of the procedure supports the continuation of our current policies in such high-risk patients.

Which therapeutic option in 2007?

Before the completion of randomized studies we can only make some recommendations with no evidence-based medical strategies. A nationwide randomized study supported by the Health Ministry should start mid 2007 in France. The aim of this study is to compare the efficacy of percutaneous PFO closure as compared to both antiplatelet and anticoagulant treatment, in 900 patients with PFO and ASA or large PFO alone, after a first cryptogenic stroke. The primary endpoint will be the rate of recurrent neurologic event on a 3-year follow-up. At the moment, our current indications for PFO closure in young patients under 60 years of age with a cryptogenic brain infarction are as following:[23]

PFO associated with ASA, because of the 4% annual risk for aspirin, PFO associated with a clinical or magnetic resonance imaging of unexplained stroke, PFO associated with recurrent brain infarction or TIA while on antithrombotic treatment, PFO associated with deep vein thrombosis before the stroke.

These indications are only local recommendations in our institution. The patient must be clearly informed of the uncertainty of the efficacy of the interventional strategy, and the necessity for a long-term clinical follow-up. Medical advances, with the development of bio-absorbable devices[24], or the use of radiofrequency allowing device-free closure(ongoing investigation) will contribute,

in the future, to improve the safety and the efficacy (with less residual shunt) of percutaneous PFO closure.

Aknowledgements

The authors gratefully thank Miss Siobhan Fisher for her secretarial assistance.

References

1 Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc 1984*;**59(1):**17-20.

2 Meissner I, Whisnant JP, Khandheria BK, et al. 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 Clinic Proced 1999*;**74(9):**62-9.

3 Bogousslavsky J, Van Melle G, Regli F. The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. *Stroke 1988*;**19(9):**1038-92.

4 Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med 1988*;**318(18):**1148-52.

5 Overell JR, Bone L, Lees KR. Interatrial septal abnormalities and stroke: a meta analysis of case-controlled studies. *Neurology* 2000;**55(8)**:1172-9.

6 Cabanes L, Mas J-L, Cohen A, et al. 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 1993*;**24(12):**1865-73.

7 Berthet K, Lavergne T, Cohen A, et al. Significant association of atrial vulnerability with atrial septal abnormalities in young patients with ischemic stroke of unknown cause. *Stroke 2000*:**31(2):**398-403.

8 Cramer SC, Rordorf G, Maki JH, et al. Increased pelvic vein thrombi in cryptogneic stroke: results from the Paradoxical Emoboli from Large Veins in Ischemic Stroke (PELVIS) study. *Stroke 2004*;**35(1):**46-50.

9 Schneider B, Hofmann T, Justen MH, Meinertz T. Chiari's network: normal anatomic variant or risk factor for arterial embolic events? *J Am Coll Cardiol 1995*;**26(1):**203-10.

10 Mas JL, Zuber M. Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. *Am Heart J 1995*;**130(5):**1083-8.

11 Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med 2001*;**345(24):**1740–6.

12 Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med 2001*;**345(20):**1444-51.

13 Homma S, Sacco RL, Di Tullio MR, et al. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation 2002*;**105(22):**2625-31.

14 Braun MU, Fassbender D, Schoen SP, et al.Transcatheter closure of patent foramen ovale in patients with cerebral ischemia. *J Am Coll Cardiol 2002*;**39(12):**2019-25.

15 Martin F, Sánchez PL, Doherty E, et al. Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Circulation 2002*;**106(9):**1121-6.

16 Alameddine F, Block PC. Transcatheter patent foramen ovale closure for secondary prevention of paradoxical embolic events: acute results from the FORECAST Registry. *Catheter Cardiovasc Interv 2004*;**62(4):**512-6.

17 Schwerzmann M, Windecker S, Wahl A, et al. Percutaneous closure of patent foramen ovale: impact of device on safety and efficacy. *Heart 2004*;**90(2):**186-90.

18 Maisel WH, Laskey WK. Patent foramen ovale closure devices. Moving beyond equipoise. *JAMA 2005*;**294(3):**366-9.

19 Windecker S, Wahl A, Nedeltchev K, et al. Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. *J Am Coll Cardiol 2004*;**44(4):**750-8.

20 Wahl A, Krumsdorf U, Meier B, et al. Transcatheter treatment of atrial septal aneurysm associated with patent foramen ovale for prevention of recurrent paradoxical embolism in high-risk patients. *J Am Coll Cardiol 2005*;**45(3):**377-80.

21 Spies C, Strasheim R, Timmermanns I, et al. Patent foramen ovale closure in patients with cryptogenic thrombo-embolic events using the Cardia PFO occluder. *Eur Heart J 2006*;**27(3):**365-71.

22 Juliard JM, Abboud H, Aubry P, et al. Percutaneous patent foramen ovale (PFO) closure in young patients with both cryptogenic brain infarction and PFO associated with atrial septal aneurysm (ASA). *EuroInterv 2006*;**2(3):**326-9.

23 Amarenco P. Patent foramen ovale and the risk of stroke: smoking gun or guilty by association ? *Heart 2005*;**91(4):**441-3.

24 Mullen MJ, Hildick-Smith D, De Giovanni JV, et al. Biostar Evaluation Study (BETS): A prospective, multicenter, phase I clinical trial to evaluate the feasibility, efficacy and safety of the Biostar bioabsorbable septal repair implant for the closure of atrial-level shunts. Circulation *2006*;**114(18):**1962-7.