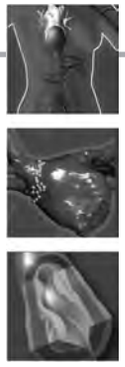

Patent foramen ovale morphology and stroke size

Evaluation of: Akhondi A, Gevorgyan R, Tseng CH *et al.*: The Association of patent foramen ovale morphology and stroke size in patients with paradoxical embolism. *Circ. Cardiovasc. Interv.* 3, 506–510 (2010). This paper evaluated the relationship between the morphological characteristics of the patent foramen ovale using echocardiography compared with cerebral infarct volume identified on MRI.

KEYWORDS: acute stroke ■ echocardiography ■ paradoxical embolism ■ patent foramen ovale ■ transcranial doppler

Vijay K Sharma

Division of Neurology, Department of Medicine, National University Hospital, 119074, Singapore
Tel.: +65 6772 2597
Fax: +65 6872 3566
drvijay@singnet.com.sg

Akhondi *et al.* have evaluated the relationship between patent foramen ovale (PFO) morphology and stroke volume [1]. Since there is no blood flow through the fetal lungs, the foramen ovale serves as an indispensable component that permits the passage of oxygenated blood from the right atrium into the left atrium. In the majority of individuals, the septum primum and secundum fuse soon after birth. However, a small communication, PFO, may persist in the region of the fossa ovalis in 15–35% of individuals [2–5] and serves as a conduit for paradoxical embolization, considered as a possible etiology for stroke in young patients with cryptogenic stroke [6]. However, whether the anatomic size of the PFO, the degree of the interatrial right-to-left shunt (RLS), concomitant atrial septal aneurysm (ASA) or the presence of a hypercoagulable state, alone or in combination, determines the highest risk of thromboembolism, remains uncertain [7,8]. A large-sized PFO, defined as greater than or equal to 2 mm in septal separation [9], has been demonstrated to be more frequent in patients with embolic strokes and PFO size greater than or equal to 4 mm is said to be an independent risk factor for recurrent cerebrovascular events [10].

Methods

This retrospective study included 72 patients with cryptogenic stroke managed at a tertiary center. MRI and transesophageal echocardiographic (TEE) findings were available for all the cases. Furthermore, extensive investigations were performed to exclude potential etiologies of stroke. TEE images were analyzed for the presence of the PFO, its length and its height of opening during the cardiac cycle. Additional cardiac structural abnormalities that were noted include the thickness of the septum secundum, excursion of the atrial septum into the right and left atria and the presence of an ASA. A saline bubble study was used to evaluate the degree of RLS. Semiquantitative RLS grade was determined, both at rest and after valsalva maneuver, in 26 patients with transcranial Doppler (TCD) saline bubble study results [11]. The authors analyzed whether any of the structural (TEE) or functional (TEE and TCD) parameters correlated with MRI stroke volumes and distribution using the Spearman correlation coefficient, two-sample t-test or the Wilcoxon rank sum test.

Results

The average age of the study subjects was 49.0 ± 16.0 years and 60% of the study population were male (43 patients). Only 13 patients were found to have hypercoagulable conditions. Anterior cicrculation infarcts were noted in 46 (64%) patients followed by posterior circulation territories in 20 (28%) patients. MRI showed infarcts in both anterior and posterior vascular territories in six (8%) patients. The median RLS grade on TEE was 2.0 (interquartile range: 1–3). ASA was detected in 12 (16.7%) patients. Although the majority (74%) of the PFOs were observed to have a left-to-right shunt on Doppler imaging, an agitated saline bubble study demonstrated the presence of RLS in 32 (45%) patients, which increased to 89% during the valsalva maneuver. It is important to note that ASA was detected in only 12 (16.7%) patients.

The most significant finding of this study was the significant relationship between the PFO size (as determined by the total septum excursion distance on TEE) and stroke

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volume on diffusion-weighted (p = 0.02) and T2-weighted (p = 0.005) MRI sequences. Another significant difference was observed between stroke volume and vascular territory, larger-volume strokes in the anterior circulation territory compared with the posterior circulation. Otherwise, no significant correlation between the TEE structural (PFO height and length and septum secundum thickness) or functional (bubble grade) parameters and the stroke volume on MRI existed. Interestingly, there was no correlation between TCD RLS grade and stroke volume with MRI.

Significance

This study contributes new information to our understanding about the etiopathogenic relationship between PFO and paradoxical cerebral embolization. Previous studies have demonstrated that patients with paradoxical embolization have larger PFOs compared with controls, as assessed by contrast transthoracic echocardiography [12], TEE [13–16], TCD [17,18] or cardiac catheterization [19]. In addition to the size of the PFO, patients with cryptogenic strokes demonstrate RLSs of higher grades [20,21]. Furthermore, it is believed that the anatomic size of the PFO might increase during the larger excursions of the atrial septum in patients with ASA. Such a phenomenon would increase the functional grade of RLSs and enhance the risk of recurrent embolic events [2,9,13].

The important question that remains uncertain and unanswered is whether the larger 'structural' or 'functional' PFOs, with or without ASA, are associated with paradoxical embolization of larger emboli and larger infarcts. Bonati *et al.* made the first attempt to address this question. In a study of 48 patients, they demonstrated that the combination of PFO plus ASA was associated with a higher likelihood of multiple ischemic lesions than PFO alone (p = 0.04). Although the PFO size was not associated with significant differences in the number of diffusion-weighted imaging lesions (p = 0.77), patients with large PFOs demonstrated a tendency of suffering from larger cerebral infarcts (p < 0.06) [22]. These findings could be interpreted to conclude that the absolute size of the PFO determined the size of the embolus traversing through it, while the presence of ASA increased the chances of paradoxical embolization, irrespective of the size of the PFO. This mechanism was proposed by De Castro *et al.*, where increased mobility of the interatrial septum was believed to enhance the probability of paradoxical embolism, by mechanically directing blood flow from the inferior vena cava through the PFO into the left atrium [23]. The claim by Akhondi *et al.* that this was the first study to establish the close relationship between the infarct size and the size of the PFO appears reasonable [1]. Perhaps, Bonati *et al.* attempted to evaluate the same relationship, but were unsuccessful owing to the insufficient sample size and measuring the diameter of the cerebral infarcts instead of the volume [22].

A higher frequency and the larger size of strokes in the anterior circulation than in the posterior circulation constitutes one of the intriguing findings of this study [1]. Conventionally, posterior circulation territories are believed to be more involved in embolic strokes [24]. To some extent, the findings by Akhondi *et al.* regarding stroke distribution make sense since the size of the stroke is determined by the size of the thrombus and large thrombi can only travel through larger PFOs and larger arteries [1]. The authors believed that the interplay of morphological and functional parameters and the size and frequency of venous thrombosis determines the dynamics of embolization through the PFO [25].

One of the most surprising findings of this study is the lack of correlation between the functional grades of RLS by TEE or TCD with the size of the infarcted territory. Since cerebral embolization of the paradoxical thrombus is the underlying mechanism for ischemic stroke, 'functional grading' of the PFO assumes immense importance. Furthermore, 'anatomical grading' of the PFO may not always be equivalent to its 'functional grading', owing to the interplay of various dynamic factors during the cardiac cycle. Jeserum *et al.*, in a study of migraine patients, demonstrated that migraineurs have higher RLS grades on TCD despite showing similar atrial septal characteristics on intracardiac echocardiography [26]. Although TEE is considered the gold standard for diagnosing PFO, it is often poorly tolerated by the patients, mostly owing to sedation [27]. Moreover, placement of endoscope in the throat affects patients' abilities to perform adequate valsalva maneuvers and, hence, the inaccurate assessment of the functional grading of the RLS by TEE could be responsible for the negative correlation observed by Akhondi *et al.* [1]. On the other hand, only a small number of patients (27) underwent TCD evaluation for RLS grading, possibly accounting for the negative correlation. TCD is a reliable technique compared with TEE and has been reported to have comparable

sensitivity and specificity [28,29]. TCD does not require sedation, impair subjects' capabilities of performing sufficient valsalva maneuvers and can be performed in different body positions to delineate the highest functional grade of the RLS. Our group has recently reported the safety and feasibility of an expanded contrast TCD protocol for detection of RLS by performing the test in different body positions [30]. We demonstrated that changing body position with repeat injections of saline contrast was well tolerated and could increase the grading of the RLS. An increased number of microbubbles traversing the PFO in the sitting position may be related to its anatomy (in addition to its morphological characteristics), located anteriorly and superiorly in the right atrium. The sitting position may cause microbubbles to rise faster in the right atrium because of their buoyancy and the increased opening of the shunt flap could permit a larger number of microbubbles to cross the RLS.

In conclusion, this study suggests that PFO size and morphology alone may not serve as reliable parameters for therapeutic decision making.

Study limitations

As acknowledged by the authors, the retrospective and observational nature of the study constitutes important limitations. In addition, the small sample size limits the important findings of this study.

Future perspective

This study demonstrated that instead of absolute values of PFO height or tunnel length, the size of the PFO (as measured by septal excursion) correlated significantly with the stroke volume. The study indicates that, in addition to the fixed anatomical parameters, structural and hemodynamic changes during the cardiac cycle may contribute significantly towards the etiopathogenic potential of a PFO. In view of the high prevalence of PFOs in the general population, selection of patients at high risk of stroke assumes great importance. Mere diagnosis of the PFO or assessment of its morphological characteristics may not be enough to identify the patients at high risk for recurrent ischemic events and for various therapeutic interventions. Failure of the recent PFO closure clinical trials to confirm the benefit in preventing strokes [31] or migraine [32], suggests that there is an urgent requirement for establishing reliable criteria for selecting high-risk patients. Perhaps this may be achieved by larger and well-designed studies that should include the assessment of the 'structural' as well as the 'functional' grading of the PFO. While the former can be assessed reliably with TEE, TCD should be employed to determine the latter.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Background

- Patent foramen ovale (PFO) is believed to provide an abnormal pathway for paradoxical embolization in patients with cryptogenic stroke. However, the most important morphological characteristic related to stroke etiology and the relationship between PFO morphology and stroke size remains uncertain.

Methods

- This retrospective observational study included 72 patients for whom the data for transesophageal echocardiography as well as MRI of the brain were available. Right-to-left shunt grade was estimated in all patients on transesophageal echocardiography and in 26 patients with transcranial Doppler. The relationship between various morphological characteristics of PFO and stroke size was also evaluated.

Results

- No significant correlation was observed between the PFO morphological parameters or right-to-left shunt grade (on transesophageal echocardiography as well as transcranial Doppler) and the infarct volume on brain MRI. Only atrial septal excursion distance was found to have a significant correlation with cerebral infarct volume ($p < 0.005$).

Significance

- This is the first study to demonstrate that the size of the cerebral infarct is related to the size of the PFO as measured by septal excursion.

Future perspective

- Larger and well-designed studies are needed for evaluating the 'structural' as well the 'functional' grading of the PFO and selecting the patients at high risk of paradoxical embolization and ischemic stroke.

Bibliography

Papers of special note have been highlighted as:
▪ of interest

1 Akhondi A, Gevorgyan R, Tseng CH *et al.*: The association of patent foramen ovale morphology and stroke size in patients with paradoxical embolism. *Circ. Cardiovasc. Interv.* 3, 506–510 (2010).

2 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.* 345, 1740–1746 (2001).

3 Schroeckenstein RF, Wasenda GJ, Edwards JE: Valvular competent patent foramen ovale in adults. *Minn. Med.* 55, 11–13 (1972).

4 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.* 59, 17–20 (1984).

5 Sweeney LJ, Rosenquist GC: The normal anatomy of the atrial septum in the human heart. *Am. Heart J.* 98, 194–199 (1979).

6 Overell JR, Bone I, Lees KR: Interatrial septal abnormalities and stroke: a meta-analysis of case–control studies. *Neurology* 55, 1172–1179 (2000).

▪ **This meta-analysis examined the association between patent foramen ovale (PFO), atrial septal aneurysm and stroke reported in various relevant case–control studies. PFO and atrial septal aneurysm were found to be significantly associated with ischemic stroke in patients younger than 55 years of age.**

7 Kizer JR, Devereux RB: Clinical practice. Patent foramen ovale in young adults with unexplained stroke. *N. Engl. J. Med.* 353, 2361–2372 (2005).

8 Wu LA, Malouf JF, Dearani JA *et al.*: Patent foramen ovale in cryptogenic stroke: current understanding and management options. *Arch. Intern. Med.* 164, 950–956 (2004).

9 Steiner MM, Di Tullio MR, Rundek T *et al.*: Patent foramen ovale size and embolic brain imaging findings among patients with ischemic stroke. *Stroke* 29, 944–948 (1998).

▪ **This study evaluated the association between brain imaging findings suggestive of embolism and PFO among ischemic stroke patients. The frequency of PFO was significantly greater among patients with cryptogenic infarcts compared with patients with determined causes of stroke (45 vs 23%; p = 0.02). Stroke locations were also found to be determined by the PFO size.**

10 Schuchlenz HW, Weihs W, Horner S, Quehenberger F: The association between the diameter of a patent foramen ovale and the risk of embolic cerebrovascular events. *Am. J. Med.* 109, 456–462 (2000).

11 Lao AY, Sharma VK, Tsivgoulis G *et al.*: Detection of right-to-left shunts: comparison between the International Consensus and Spencer Logarithmic Scale criteria. *J. Neuroimaging* 18, 402–406 (2008).

12 Webster MW, Chancellor AM, Smith HJ *et al.*: Patent foramen ovale in young stroke patients. *Lancet* 2, 11–12 (1988).

13 Homma S, Di Tullio MR, Sacco RL, Mihalatos D, Li MG, Mohr JP: Characteristics of patent foramen ovale associated with cryptogenic stroke. A biplane transesophageal echocardiographic study. *Stroke* 25, 582–586 (1994).

14 Hausmann D, Mugge A, Daniel WG: Identification of patent foramen ovale permitting paradoxic embolism. *J. Am. Coll. Cardiol.* 26, 1030–1038 (1995).

15 Van CG, Schulze D, Cosyns B, Vandenbossche JL: Relation between patent foramen ovale and unexplained stroke. *Am. J. Cardiol.* 71, 596–598 (1993).

16 Goel SS, Tuzcu EM, Shishehbor MH *et al.*: Morphology of the patent foramen ovale in asymptomatic versus symptomatic (stroke or transient ischemic attack) patients. *Am. J. Cardiol.* 103, 124–129 (2009).

17 Serena J, Segura T, Perez-Ayuso MJ, Bassaganyas J, Molins A, Davalos A: The need to quantify right-to-left shunt in acute ischemic stroke: a case control study. *Stroke* 29, 1322–1328 (1998).

▪ **This study aimed to determine whether right-to-left shunt (RLS) grade on transcranial Doppler (TCD) determines the stroke risk. Detection of large-grade RLS was associated with a higher risk of stroke (odds ratio: 3.5; 95% CI: 1.29–9.87), particularly with cryptogenic stroke (odds ratio: 12.4; 95% CI: 4.08–38.09) after adjustment for concomitant vascular risk factors.**

18 Jauss M, Kaps M, Keberle M, Haberbosch W, Dorndorf W: A comparison of transesophageal echocardiography and transcranial Doppler sonography with contrast medium for detection of patent foramen ovale. *Stroke* 25, 1265–1267 (1994).

19 Bridges ND, Hellenbrand W, Latson L, Filiano J, Newburger JW, Lock JE: Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. *Circulation* 86, 1902–1908 (1992).

20 Webster MW, Chancellor AM, Smith HJ *et al.*: Patent foramen ovale in young stroke patients. *Lancet* 2, 11–12 (1988).

21 Overell JR, Bone I, Lees KR: Interatrial septal abnormalities and stroke: a meta-analysis of case–control studies. *Neurology* 55, 1172–1179 (2000).

22 Bonati LH, Kessel-Schaefer A, Linka AZ *et al.*: Diffusion-weighted imaging in stroke attributable to patent foramen ovale: significance of concomitant atrial septum aneurysm. *Stroke* 37, 2030–2034 (2006).

23 De Castro S, Cartoni D, Fiorelli M *et al.*: Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke* 31, 2407–2413 (2000).

24 Venketasubramanian N, Sacco RL, Di Tullio M, Sherman D, Homma S, Mohr JP: Vascular distribution of paradoxical emboli by transcranial Doppler. *Neurology* 43, 1533–1535 (1993).

25 Hausmann D, Mugge A, Daniel WG: Identification of patent foramen ovale permitting paradoxic embolism. *J. Am. Coll. Cardiol.* 26, 1030–1038 (1995).

26 Jesurum JT, Fuller CJ, Velez CA *et al.*: Migraineurs with patent foramen ovale have larger right-to-left shunt despite similar atrial septal characteristics. *J. Headache Pain* 8, 209–216 (2007).

▪ **This retrospective study evaluated the differences in RLS and atrial septal characteristics between migraineurs and non-migraineurs referred for transcatheter closure of PFO. Intracardiac echocardiography was used to assess atrial septal characteristics. Migraineurs had significantly higher RLS grades than non-migraineurs. However, atrial septal characteristics were similar between groups.**

27 Natanzon A, Goldman ME: Patent foramen ovale: anatomy versus pathophysiology which determines stroke risk? *J. Am. Soc. Echocardiogr.* 16, 71–76 (2003).

28 Jauss M, Kaps M, Keberle M *et al.*: A comparison of transesophageal echocardiography and transcranial Doppler sonography with contrast medium in the detection of patent foramen ovale. *Stroke* 25, 1265–1267 (1994).

29 Job FP, Ringelstein EB, Grafen Y *et al.*: Comparison of transcranial contrast Doppler sonography and transesophageal contrast echocardiography for the detection of patent foramen ovale in young stroke patients. *Am. J. Cardiol.* 74, 381–384 (1994).

30 Lao AY, Sharma VK, Tsivgoulis G, Malkoff MD, Alexandrov AV, Frey JL: Effect of body positioning during transcranial Doppler detection of right-to-left shunts. *Eur. J. Neurol.* 14, 1035–1039 (2007).

▪ **This study evaluated an expanded TCD protocol to evaluate the effect of different body positions on RLS detection or grading. Changes in body position and additional agitated saline injections were tolerated. The highest microbubble yield was achieved in the upright sitting position. The study suggested that the functional grade of RLS might differ in various body positions, a finding that could explain the discrepancies observed between trans-esophageal echocardiographic and TCD testing for RLS.**

31 Krasuski RA, Hart SA, Allen D *et al.*: Prevalence and repair of intraoperatively diagnosed patent foramen ovale and association with perioperative outcomes and long-term survival. *JAMA* 302, 290–297 (2009).

32 Dowson A, Mullen MJ, Peatfield R *et al.*: Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. *Circulation* 117, 1397–1404 (2008).