Clinical Investigation

Importance of Persistent Right-to-Left Shunt

After Patent Foramen Ovale Closure in Cryptogenic Stroke Patients

Lu He, PhD
Gesheng Cheng, MD
Yajuan Du, MD
Yushun Zhang, MD, PhD

Percutaneous closure of patent foramen ovale (PFO) is widely performed to prevent recurrent stroke or transient ischemic attack in patients with cryptogenic stroke. However, the influence of different degrees of right-to-left shunting (RLS) has rarely been reported.

We retrospectively evaluated the cases of 268 patients with cryptogenic stroke who underwent PFO closure at our hospital from April 2012 through April 2015. In accordance with RLS severity, we divided the patients into 2 groups: persistent RLS during normal breathing and the Valsalva maneuver (n=112) and RLS only during the Valsalva maneuver (n=156). Baseline characteristics, morphologic features, and procedural and follow-up data were reviewed. The primary endpoint was stroke or transient ischemic attack.

*More patients in the persistent group had multiple or bilateral ischemic lesions, as well as a larger median PFO diameter (2.5 mm [range, 1.8–3.9 mm]) than did patients in the Valsalva maneuver group (1.3 mm [range, 0.9–1.9 mm]) (*P *<0.001). Atrial septal aneurysm was more frequent in the persistent group: 25 patients (22.3%) compared with 18 (11.5%) (*P*=0.018). Three patients in the persistent group had residual shunting. The annual risk of recurrent ischemic stroke was similar between groups: 0.298% (persistent) and 0.214% (Valsalva maneuver).*

Our findings suggest that patients with persistent RLS have more numerous severe ischemic lesions, larger PFOs, and a higher incidence of atrial septal aneurysm than do those without. Although our persistent group had a greater risk of residual shunting after PFO closure, recurrence of ischemic events did not differ significantly from that in the Valsalva maneuver group. ***(Tex Heart Inst J 2020;47(4):244-9)***

Key words: *Embolism/etiology/prevention & control; foramen ovale, patent/complications/diagnostic imaging/surgery/therapy; heart atria/abnormalities/complications; ischemic attack, transient/etiology/prevention & control; recurrence; retrospective studies; risk factors; secondary prevention; stroke/prevention & control; treatment outcome*

From: *Department of Structural Heart Disease, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710068, People's Republic of China*

Address for reprints:
Yushun Zhang, MD, PhD, Department of Structural Heart Disease, The First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Rd., Xi'an 710068, PRC

E-mail: *zys2889@sina.com*

Postnatal failure of the septum primum and secundum to fuse results in a patent foramen ovale (PFO). This valvelike, usually tunnel-shaped opening, observed in approximately 25% of the general population,[1] occurs between the fibrous, thin, mobile septum primum and the muscular septum secundum. No concomitant anatomic septal defect is evident on transesophageal echocardiograms (TEE). Much has been written about interatrial communications, but a research gap exists regarding relationships between PFO morphology and degrees of right-to-left shunting (RLS).[2,3] Currently, PFO closure by device implantation is widely performed to prevent recurrent ischemic stroke in patients with cryptogenic stroke (CS) who are candidates for percutaneous interventional therapy.[4-6] However, understanding the relationship between PFO morphology and the degree of RLS is necessary for successful PFO closure.[7,8]

Studies of shunt grade have produced contrasting data on the risks associated with persistent RLS.[9-11] The anatomic and functional characteristics of PFO that increase the risk of recurrent stroke are poorly understood. Therefore, we compared differences in PFO morphology and follow-up data among 2 groups of CS patients who had RLS of varying severity.

Patients and Methods

We identified 268 patients younger than 60 years of age who were diagnosed with CS and underwent PFO closure at our hospital from April 2012 through April 2015. All the patients met the current standard indications for undergoing percutaneous transcatheter PFO closure.[12] Before the procedure, they underwent preoperative contrast transthoracic echocardiography (TTE), TEE, and either computed tomography (CT) or magnetic resonance imaging (MRI); PFO closure was fluoroscopically guided. Stroke was defined as a focal neurologic deficit resulting from cerebral ischemia with a neuroanatomically relevant infarct on images or in accordance with symptoms lasting >24 hours.[13]

The patients gave written informed consent, and the local ethics committee approved this study. In accordance with degree of RLS, we divided the cohort into 2 groups: a persistent group (112 patients who had RLS on TTE during normal breathing and the Valsalva maneuver [VM]), and a VM group (156 who had RLS only during the VM). The groups' baseline characteristics were similar except that more patients in the persistent group had multiple or bilateral ischemic brain lesions (Table I). We reviewed morphologic features, procedural data, and follow-up data.

Echocardiographic Protocols and Definitions

The Vivid E9 color-Doppler ultrasound system (GE Healthcare) with a 2- to 4-MHz transducer was used to perform TTE, and a 4- to 7-MHz transducer was used for TEE. The apical 4-chamber view was generally selected. All right atrial and interatrial septal characteristics were recorded, including PFO diameters and tunnel length, as well as atrial septal aneurysm (ASA), prominent eustachian valve, or a Chiari network (Fig. 1).

We defined PFO diameter as the maximum distance between the septum primum and secundum. Tunnel length was the maximum overlap of the septum primum and secundum. An ASA was defined as the excursion of the septum primum into the atria exceeding 10 mm or total excursion distance exceeding 15 mm.[14] If a soft atrial septum precluded clear diagnosis of ASA, we recorded whether the atrial septal excursion distance exceeded 6.5 mm (an indication of septal mobility). The eustachian valve was measured for prominence from the end of the muscular ridge to the free-floating end in the right atrium.[15,16] A Chiari network was diagnosed when coarse or fine fibers were seen in the right atrium.[17] The fibers originated from the eustachian or a Thebesian valve at the orifice of the inferior vena cava or at the coronary sinus and were attached to the upper right atrial wall or the interatrial septum.

Evaluating RLS is subjective. We confirmed RLS when microbubbles (MBs) were seen in the left atrium within the first 3 cardiac cycles after contrast appeared in the right atrium during normal respiration or the VM. We ranked RLS severity on a 4-level scale: level 1 indicated that no MBs appeared in the left atrium in any image frame (no RLS); level 2, ≤10 MBs (mild RLS); level 3, 11 to 30 MBs (moderate RLS); and level 4, >30 MBs (severe RLS).[18]

Patent Foramen Ovale Closure

The patients were given intravenous antibiotics one hour before the PFO closure procedure and local anesthesia when the procedure started. The operator determined device size in accordance with the characteristics of each PFO. The Amplatzer PFO Occluder (St. Jude Medical, part of Abbott) was always used. Device implantation was guided by fluoroscopy only, through the right femoral vein. Heparin (80–100 IU/kg) was administered in accordance with each patient's body weight. Within 24 hours postprocedurally, all patients underwent TTE examination for early residual shunting and pericardial effusion. Therapy involved low-molecular-weight heparin (10 U/kg · hr for 48 hr), clopidogrel (50–75 mg/d for 3 mo), and aspirin (100 mg/d for 6 mo).

Follow-Up

All patients were monitored 1, 3, 6, and 12 months after device implantation and then yearly thereafter. At one month, Holter monitoring and TTE were performed

TABLE I. Baseline Characteristics of the Study Groups

Variable	Persistent Group (n=112)	VM Group (n=156)	*P* Value
Age (yr)	43 (39–54)	45.5 (35–51)	0.439
Weight (kg)	67.8 ± 11.2	65.2 ± 18.5	0.073
Male	65 (58)	72 (46.2)	0.055
Hypertension	12 (10.7)	15 (9.6)	0.768
Diabetes mellitus	6 (5.4)	9 (5.8)	0.885
Hyperlipidemia	16 (14.3)	19 (12.2)	0.614
History of smoking	52 (46.4)	59 (37.8)	0.158
Mutation methylenetetrahydrofolate reductase	21 (18.8)	24 (15.4)	0.467
Hyperhomocysteinemia	12 (10.7)	16 (10.3)	0.904
Multiple or bilateral ischemic lesions on CT or MRI	90 (80.4)	101 (64.7)	0.005

CT = computed tomography; MRI = magnetic resonance imaging; VM = Valsalva maneuver

Data are presented as median and interquartile range, as mean ± SD, or as number and percentage. P <0.05 was considered statistically significant.

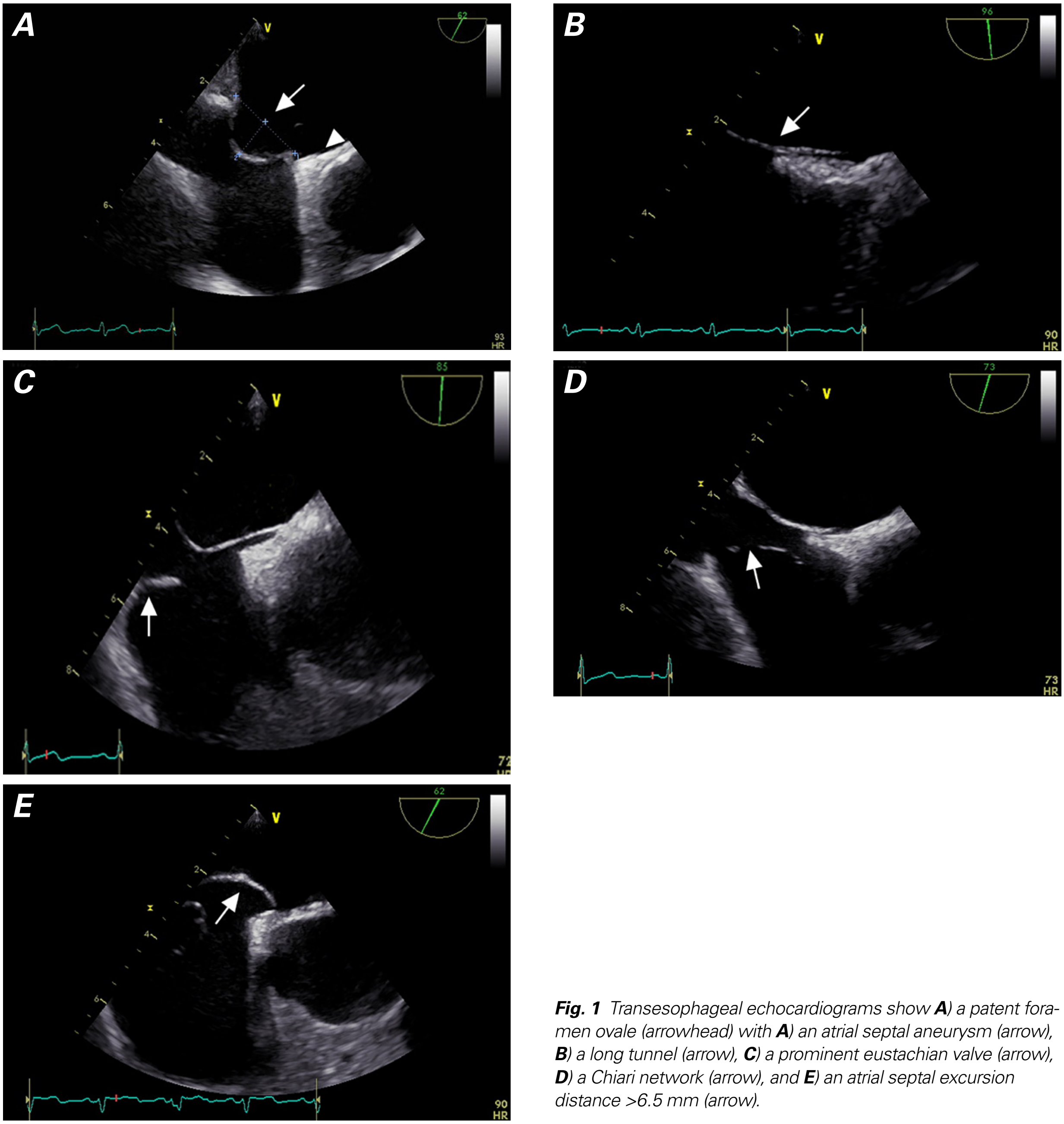

Fig. 1 Transesophageal echocardiograms show **A**) a patent foramen ovale (arrowhead) with **A**) an atrial septal aneurysm (arrow), **B**) a long tunnel (arrow), **C**) a prominent eustachian valve (arrow), **D**) a Chiari network (arrow), and **E**) an atrial septal excursion distance >6.5 mm (arrow).

to detect atrial fibrillation or device embolization. At 3 months, contrast TTE was performed to detect residual RLS. If none was seen, no contrast TTE was necessary thereafter. Otherwise, patients underwent contrast TTE 6 months after the procedure. All were monitored through telephone questionnaires or during office visits with cardiovascular and neurologic specialists. When patients had palpitations or chest pain, Holter monitoring and electrocardiography were performed. Follow-up was completed by 30 April 2017.

Statistical Analysis

Data were analyzed with use of SPSS 19.0 for Windows (SPSS, an IBM company). Normally distributed quantitative variables were presented as mean ± SD. Differences in means for continuous variables were compared by using the Student *t* test. For nonnormally distributed variables, we used median and interquartile range and compared differences in median by using the Mann-Whitney U test. Categorical data were presented as number and percentage. We used the χ^2 or Fisher exact test for 2-group comparisons. P values <0.05 were considered statistically significant.

Results

The median PFO diameter in the persistent group, 2.5 mm (range, 1.8–3.9), was larger than that of 1.3 mm (range, 0.9–1.9) in the VM group (*P* <0.001). Twenty-five patients in the persistent group (22.3%) had ASA, compared with 18 patients in the VM group (1.5%) (*P* <0.018). Nine in the persistent group (8%) had an atrial septal excursion distance >6.5 mm, compared with 3 (1.9%) in the VM group (*P*=0.017) (Table II).

Technical success (device deployment) and procedural success (no major in-hospital adverse events) were achieved in all the patients (Table III). Procedural complications included 2 arteriovenous fistulae (one per group), 2 pseudoaneurysms (one per group), and an inguinal hematoma (persistent group).

The mean follow-up time was 3.1 ± 1 years. At 6 months, we detected residual RLS in 3 patients in the persistent group and none in VM patients. One patient in the persistent group died of lung cancer during the study period.

The rates of recurrent stroke or TIA per 100 patient-years were 0.298% in the persistent group and 0.214% in the VM group (no difference in risk). Multivariate logistic regression, adjusted simultaneously for age and sex, produced an odds ratio of 0.787 (95% CI, 0.046–13.468; *P*=0.869). Transient ischemic attack recurred in one patient in the persistent group (at 1 mo) and one in the VM group (at 3 mo). The first had trace RLS but the second had none, suggesting an alternative cause of the TIA. In the persistent group, 2 patients (1.8%) had paroxysmal atrial fibrillation (at 2 wk and 3 mo, respectively); sinus rhythm resumed spontaneously in the first and after pharmacologic conversion in the second. We observed no occluder translocation, erosion, pericardial effusion, or puncture-site bleeding.

Discussion

Although PFO in patients with CS has been widely treated, few relevant reports on the significance of persistent RLS have been published. Our study revealed degrees of causality: persistent RLS was associated with multiple and bilateral ischemic lesions and larger PFOs, and its association with ASA and greater atrial septal excursion distance may relate to more cases of residual shunting after PFO closure.

TABLE II. Comparison of Patent Foramen Ovale Morphology Between the Study Groups

Variable	Persistent Group (n=112)	VM Group (n=156)	*P* Value
PFO diameter (mm)	2.5 (1.8–3.9)	1.3 (0.9–1.9)	<0.001
Tunnel length (mm)	6.8 (5–8.4)	6.9 (5.3–8.3)	0.779
Atrial septal aneurysm	25 (22.3)	18 (11.5)	0.018
Atrial septal excursion distance >6.5 mm	9 (8)	3 (1.9)	0.017
Prominent eustachian valve	2 (1.8)	3 (1.9)	0.9999
Chiari network	3 (2.7)	4 (2.6)	0.9999

PFO = patent foramen ovale; VM = Valsalva maneuver

Data are presented as median and interquartile range or as number and percentage. *P* <0.05 was considered statistically significant.

TABLE III. Procedural Characteristics

Variable	Persistent Group (n=112)	VM Group (n=156)	*P* Value
Systolic PAP (mmHg)	21 (19–23)	20 (19–22)	0.02
Mean PAP (mmHg)	13 (12–14)	13 (12–13)	0.646
Procedure time (min)	20 (19–25)	22 (22–25)	0.034
Fluoroscopy time (min)	3 (2–3)	3 (3–3)	0.227
Procedural complications	—	—	0.954
Arteriovenous fistula	1 (0.9)	1 (0.6)	—
Pseudoaneurysm	1 (0.9)	1 (0.6)	—
Hematoma	1 (0.9)	0	—

PAP = pulmonary artery pressure; VM = Valsalva maneuver

Data are presented as median and interquartile range or as number and percentage. *P* <0.05 was considered statistically significant.

Rates of technical and procedural success were 100% in both groups.

Severe RLS and larger PFO openings have been identified as the chief contributors to paradoxical embolism in stroke patients.[19-22] However, PFOs can be short or angular, and they may have other anatomic characteristics that complicate measuring the opening. Moreover, the maximal shunting that usually occurs during the VM cannot always be obtained in stroke patients, and the type and level of strain almost always differ. Therefore, determining the presence of persistent RLS (during normal breathing and VM) is crucial.

In our study, patients with persistent RLS were more likely to have multiple and bilateral ischemic brain lesions on MRI and CT, as Rigatelli and colleagues reported.[11] Our findings that the severity of strokes in patients with persistent RLS is greater than in those without it indicate that persistent RLS is an independent risk factor. Presumably, patients with persistent RLS are at risk of paradoxical embolism for longer time periods than are patients whose RLS is induced only by the VM.[23]

Tunnel length, prominent eustachian valves, and presence of Chiari networks did not differ significantly between groups, suggesting that some but not all morphologic features of PFO and concomitant septal abnormalities influence the cause of CS. Schuchlenz and colleagues[24] reported that larger PFOs and higher-degree RLS correlated with a higher incidence of paradoxical embolism. The risks of initial and recurrent TIA and ischemic stroke increased significantly with PFO diameters >4 mm; furthermore, the severity of RLS increased accordingly with larger PFO diameter. In addition, we found that ASA and atrial septal excursion distance >6.5 mm correlate with PFO diameter, so a mobile interatrial septum may indicate persistent RLS. Finally, our finding that patients with persistent RLS are more likely to have multiple or bilateral ischemic strokes is consistent with previous studies in which PFO-associated ASA increased stroke severity.[25,26]

The residual RLS in our persistent group indicates the importance of carefully characterizing larger, more complex PFOs before guiding and deploying the occluder in these patients, as well as evaluating them post-procedurally. However, despite varying PFO anatomies between groups, we found no significant difference in annual risk of recurrent TIA or ischemic stroke. Two explanations may apply. First, although the PFOs differed anatomically on TEE, our goal was to determine which occluder size would best reduce each patient's risk of residual RLS. Second, our study's relatively short 3.1-year follow-up time was perhaps not long enough for all instances of embolization to recur, leading to the lack of significant differences in stroke recurrence rates between groups.

Limitations. The limitations of our study include its single-institution, retrospective, nonrandomized design, which may have introduced selection bias. In addition to the small sample size, the follow-up time of 3.1 years may have been too short for all embolic events to develop. Studies that include larger numbers of patients and longer follow-up times are needed to generate a substantial clinical message.

Conclusions

Our study suggests that, among patients undergoing PFO closure for CS, those with persistent RLS have greater numbers of severe ischemic lesions, larger PFOs, greater atrial septal excursion distances, and higher incidences of ASA than do patients without persistent RLS. Although our persistent group had a greater risk of residual RLS after PFO closure than did our VM group, the rates of recurrent stroke or TIA did not differ significantly.

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. Onorato E, Casilli F. Influence of PFO anatomy on successful transcatheter closure. Interv Cardiol Clin 2013;2(1):51-84.
3. McKenzie JA, Edwards WD, Hagler DJ. Anatomy of the patent foramen ovale for the interventionalist. Catheter Cardiovasc Interv 2009;73(6):821-6.
4. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med 2012;366(11):991-9.
5. Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med 2013;368(12):1092-100.
6. Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med 2013;368(12):1083-91.
7. Meier B. Closure of patent foramen ovale: technique, pitfalls, complications, and follow up. Heart 2005;91(4):444-8.
8. Ho SY, McCarthy KP, Rigby ML. Morphological features pertinent to interventional closure of patent oval foramen. J Interv Cardiol 2003;16(1):33-8.
9. Anzola GP, Morandi E, Casilli F, Onorato E. Different degrees of right-to-left shunting predict migraine and stroke: data from 420 patients. Neurology 2006;66(5):765-7.
10. Giardini A, Donti A, Formigari R, Salomone L, Palareti G, Guidetti D, Picchio FM. Spontaneous large right-to-left shunt and migraine headaches with aura are risk factors for recurrent stroke in patients with a patent foramen ovale. Int J Cardiol 2007;120(3):357-62.
11. Rigatelli G, Dell'Avvocata F, Cardaioli P, Giordan M, Braggion G, Aggio S, et al. Permanent right-to-left shunt is the key factor in managing patent foramen ovale. J Am Coll Cardiol 2011;58(21):2257-61.
12. Inzitari D. The Italian Guidelines for stroke prevention. The Stroke Prevention and Educational Awareness Diffusion (SPREAD) Collaboration. Neurol Sci 2000;21(1):5-12.
13. A classification and outline of cerebrovascular diseases. II. Stroke 1975;6(5):564-616.

14. Agmon Y, Khanderia BK, Meissner I, Gentile F, Whisnant JP, Sicks JD, et al. Frequency of atrial septal aneurysms in patients with cerebral ischemic events. Circulation 1999;99(15):1942-4.
15. Kydd AC, McNab D, Calvert PA, Hoole SP, Rekhraj S, Sievert H, et al. The eustachian ridge: not an innocent bystander. JACC Cardiovasc Imaging 2014;7(10):1062-3.
16. Schuchlenz HW, Saurer G, Weihs W, Rehak P. Persisting eustachian valve in adults: relation to patent foramen ovale and cerebrovascular events. J Am Soc Echocardiogr 2004;17(3):231-3.
17. 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.
18. Zhao E, Wei Y, Zhang Y, Zhai N, Zhao P, Liu B. A comparison of transthoracic echocardiography and transcranial Doppler with contrast agent for detection of patent foramen ovale with or without the Valsalva maneuver. Medicine (Baltimore) 2015;94(43):e1937.
19. Steiner MM, Di Tullio MR, Rundek T, Gan R, Chen X, Liguori C, et al. Patent foramen ovale size and embolic brain imaging findings among patients with ischemic stroke. Stroke 1998;29(5):944-8.
20. 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 1998;29(7):1322-8.
21. Van Camp G, Schulze D, Cosyns B, Vandenbossche JL. Relation between patent foramen ovale and unexplained stroke. Am J Cardiol 1993;71(7):596-8.
22. Stone DA, Godard J, Corretti MC, Kittner SJ, Sample C, Price TR, Plotnick GD. Patent foramen ovale: association between the degree of shunt by contrast transesophageal echocardiography and the risk of future ischemic neurologic events. Am Heart J 1996;131(1):158-61.
23. Ranoux D, Cohen A, Cabanes L, Amarenco P, Bousser MG, Mas JL. Patent foramen ovale: is stroke due to paradoxical embolism? Stroke 1993;24(1):31-4.
24. 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 2000;109(6):456-62.
25. Comess KA, DeRook FA, Beach KW, Lytle NJ, Golby AJ, Albers GW. Transesophageal echocardiography and carotid ultrasound in patients with cerebral ischemia: prevalence of findings and recurrent stroke risk. J Am Coll Cardiol 1994;23(7):1598-603.
26. Cabanes L, Mas JL, Cohen A, Amarenco P, Cabanes PA, Oubary P, 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.