



# Patent Foramen Ovale in Young Adults with Cryptogenic Stroke or Transient Ischemic Attack

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## Abstract

**Background:** Stroke, one of the most important causes of morbidity and mortality in the world, is of great importance in young adults (15-45 years), amongst whom the causes of stroke and transient ischemic attack (TIA) are different from those in older ages and a significant portion of them have no known etiology. Patent foramen ovale (PFO) is considered a probable cause in this group.

**Methods:** Patients between 15 and 45 years of age with TIA or stroke were examined and evaluated for causes of cerebrovascular accidents. Patients with no definite cause for stroke or TIA, except for PFO, despite our extensive evaluations were categorized as cryptogenic. The controls were comprised of those between 15 and 45 years old who underwent transesophageal echocardiography (TEE) for reasons other than stroke. The frequency of PFO and its characteristics were compared between the two groups.

**Results:** The case group comprised 48 patients with cryptogenic stroke (n=31) and TIA (n=17), and the control group consisted of 57 patients. The age distribution of the groups was normal, and there was no significant difference between the age and gender of the two groups. The frequency of PFO in the case and control groups was 52% and 25%, respectively (p value=0.003, odds ratio=3.33, confidence interval=1.46-7.63). The exaggerated motion of the interatrial septum (IAS) in the case and control groups was 18.8% and 0%, respectively. Right-to-left shunt at rest in the case and control groups was 78% and 28%, respectively (significant differences). The differences in terms of PFO size, number of bubbles, and atrial septal aneurysm were not significant between the two groups.

**Conclusion:** PFO had a relation with stroke and TIA in the young adults, and right-to-left shunt at rest and exaggerated motion of the IAS could increase the possibility of paradoxical emboli. It seems that the presence of atrial septal aneurysm, number of bubbles, and PFO size did not increase the risk of cerebrovascular accidents.

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**Keywords:** Foramen ovale, patent • Stroke • Ischemic attack, transient • Echocardiography, transesophageal

## Introduction

Stroke is one of the most important causes of morbidity and mortality in the world and has a great importance in young adults (15-45 years). The causes of stroke in this age

group are different from those in older ages; large vessel atherosclerosis, cardioembolism, and intracranial small vessel disease, which cause about 95 percent of strokes in all age groups, constitute only about 50 percent of the causes of ischemic strokes in young adults<sup>1-3</sup> and approximately 43%

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of strokes in young adults are cryptogenic strokes, i.e. they do not have a definite cause despite extensive evaluations.<sup>4</sup> Stroke also leads to severe physical, psychosocial, and economic detriments in this group.

Recent advances in imaging and transesophageal echocardiography (TEE) have demonstrated that the frequency of patent foramen ovale (PFO) is higher in patients with cryptogenic stroke.<sup>5-8</sup>

A meta-analysis of case-control studies has shown a strong association between PFO and cryptogenic stroke in patients under the age of 55 years;<sup>8</sup> however, since about 25% of the population are believed to have PFO,<sup>9</sup> the mere association of PFO with stroke is not enough to establish the diagnosis of paradoxical embolism.

Transient ischemic attack (TIA) is of unknown etiology in many patients,<sup>10</sup> and a diagnosis of the causes is of significant importance for the prevention of stroke. PFO has been regarded as one of the causes of TIA in recent years.<sup>11</sup>

Cryptogenic stroke secondary to paradoxical embolism, nevertheless, has hitherto remained a matter of debate. The pathophysiological mechanisms and the morphological and functional characteristics of PFO have yet to be satisfactorily determined as do the factors causing stroke in patients with PFO and the optimum treatment in these patients.

With the above queries in mind, we conducted this prospective study in young patients with stroke of unknown etiology.

## Methods

In this case-control study, conducted with simple sampling between March 2006 and August 2008, we evaluated young adult patients with stroke or TIA in Ghaem Hospital, Mashhad, Iran.

TIA was defined as a focal neurological defect with a vascular origin that initiated suddenly and improved in less than 24 hours, and stroke was defined as focal neurological signs or symptoms that had initiated suddenly and lasted more than 24 hours and their vascular origin was documented by brain imaging (CT scan or MRI).<sup>12</sup>

The patients were examined by a neurologist, and the types of neurological defects and brain imaging findings were recorded. The baseline information of the patients, consisting of age, gender, vascular risk factors, signs and symptoms of deep vein thrombosis, oral contraceptive consumption, and relation between the initial time of stroke or TIA with the Valsalva maneuver (e.g. weight lifting, straining for bowel movements, vomiting, sexual intercourse, and coughing), were recorded.

Blood evaluations were composed of standard blood tests, coagulative state evaluation (protein S deficiency, protein C deficiency, anticardiolipin, and lupus anticoagulant); and if necessary, tests for collagen vascular disease were carried

out. Color Doppler sonography of carotids and vertebral arteries and transcranial Doppler sonography were carried out for all the patients so as to assess vascular diseases.

Cardiac evaluations comprised physical examination, 12-lead ECG, transthoracic echocardiography (TTE), and TEE with agitated saline injections performed by an echocardiography specialist for all the patients. Agitated saline injections were done 3 times for each patient (once at rest and twice with Valsalva maneuver). Echocardiography was carried out with vivid 7 (GE Vingmed Ultrasound, Hortem, Norway) Machine with an M3S multi-frequency transducer for TTE and 7.5 MHz multiplanar for TEE.

PFO was diagnosed when at least 3 microbubbles were identified in the left atrium within 3 cardiac cycles from the full opacification of the right atrium.<sup>13</sup> Atrial septal aneurysm was defined as an abnormally redundant interatrial septum with an excursion of  $\geq 11$  mm into the right or left atrium and a base span of at least 15 mm.<sup>14,15</sup> Exaggerated motion of the interatrial septum (IAS) was defined as the motion of the IAS more than 6.5mm and less than 11mm.<sup>16</sup> PFO <2mm was considered as small, between 2 to 6.5mm as moderate, and  $\geq 6.5$ mm as large.<sup>14</sup> The passing of 10 bubbles or more was considered as high risk and fewer than 10 bubbles as low risk.

Patients with no definite cause for stroke or TIA, except for PFO, despite our extensive evaluations were categorized as cryptogenic. The control group was comprised of 15 to 45-year-old consecutive patients who underwent TEE due to causes other than stroke and TIA (evaluating rheumatismal valvular disease and left atrial mass and ruling out aortic dissection and pulmonary thromboembolism) (none of them had congenital heart disease).

The two groups were analyzed with SPSS version 11.5, and the normal distribution of the variables was tested using the Kolmogorov-Smirnov 1-sample test. The comparisons between the qualitative variables were done using the  $\chi^2$  test and Fisher exact test. The non-parametric Mann-Whitney test was utilized to compare the two groups with nominal variables. A P value less than 0.05 was considered significant.

## Results

The baseline characteristics of the two groups are documented in Table 1. The age distribution in both groups was normal, and the two groups were identical in gender and age.

Stroke was detected in 31 patients and TIA in 17. Thirty-seven patients suffered cerebrovascular accident during sleep or wakefulness but without the Valsalva maneuver, and 11 patients had the Valsalva maneuver simultaneously or just before the accident. Nine (36%) patients had PFO, and only 2 (8.7%) did not have PFO. Two patients had clinical and



sonographic evidence of deep vein thrombosis. Four patients were oral contraceptive pills consumers, but coagulation tests showed no disorder in all the patients.

In total, 37.5% of the patients had vascular risk factors, including hypertension 16.3%, smoking 18.8%, hyperlipidemia 4.2%, and diabetes 2.1%.

Fifteen (33.3%) patients in the case group and 8 (16%) patients in the control group showed PFO in TTE (p value=0.017), but the size difference of the PFO between the two groups was not significant. The results of the TEE assessments are documented in Table 2.

The presence of atrial septal aneurysm was more common in the case group (16.7% in comparison with 5.4%); the

Table 1. Baseline information and risk factors of the patients

	Patients (n=48)	Control (n=57)
Men	25	27
Women	23	30
Mean age (y)	34.8±9.4	33±9.8
Range of age (y)	17-45	15-45

Table 2. Comparison of TEE findings between the two groups

	Patients N=48	Controls N=57	p value	Odds ratio	Confidence interval
Presence of patent foramen ovale	25(52%)	14(25%)	0.003	3.33	1.46-7.63
Size of patent foramen ovale	14 small (56%), 10 moderate (40 %), 1 large (4 %)	11 small (79 %), 3 moderate (21 %), 0 large	0.231	-	-
Atrial septal aneurysm	8(16.7%)		0.060	3.53	0.88-14.17
Exaggerated motion of interatrial septum	9(18.8%)	0	0.001	2.46	1.93-3.13
Shunt at rest	18 (72%)	6 (43%)	0.007	8	1.73-4.75
More than 10 bubbles	16 (64 %)	9 (64%)	0.633	-	-

difference, however, was not significant. The frequency of PFO was 52.17% in the women and 52% in the men. In the TIA patients, the PFO frequency was 52.9%, which had a significant difference with the control group (25%) (p value=0.034, odds ratio=3.37, confidence interval 1.09-10.42).

## Discussion

The relation between PFO and cryptogenic stroke and TIA has been confirmed by many recent studies.<sup>17-21</sup> Be that as it may, the said relation in young adults has yet to be thoroughly assessed. The present study showed the relation between PFO and cryptogenic stroke and TIA in young adults. There was also a relation between the presence of right-to-left shunt at rest (passing the bubbles at rest) and the exaggerated motion of the IAS with the stroke and TIA.

Dolores et al. demonstrated that the frequency of PFO in patients younger than 50 years old with cryptogenic stroke was 41.8%.<sup>20</sup> In the Nedeltchev et al. study with patients at a mean age of 52±13 years, the frequency of PFO was 38% in the men and 28% in the women.<sup>19</sup> Ozcan et al. assessed

all ages and reported the frequency of PFO to be 51%.<sup>18</sup> The similar results in these studies and ours denote a significant difference with respect to the PFO frequency between the patient group and controls. In our study, like the Dolores et al. and Natanzon et al. studies, there was no relation between the size of PFO and stroke;<sup>20,21</sup> but in a study by Sachin et al., there was a relation between the size of PFO and the paradoxical emboli.<sup>22</sup> It is worthy of note, however, that the categorization of the PFO size in the foregoing study differed from that in ours. Sachin et al. considered PFO >4mm as large and less than 4mm as small.

The presence of right-to-left shunt at rest was related to cryptogenic stroke in other studies as well as in our study.<sup>20,23</sup> The number of bubbles is said to be related to stroke in some studies;<sup>21,22</sup> that was not the case in our study, however.

The exaggerated motion of the IAS in our study was a risk factor for stroke and TIA, and this relation has been reported by previous studies as well.<sup>20,23</sup>

There is still controversy over the coincidence of atrial septal aneurysm with PFO in the creation of stroke. Whereas

some authors have reported no relevance<sup>20,21</sup> as was the case in our study, Sachin et al. have provided evidence to the contrary.<sup>22</sup>

The role of the Valsalva maneuver in the induction of emboli via PFO was remarkable in our study insofar as 34% of the patients with PFO had the Valsalva maneuver simultaneously or just before cerebrovascular accident and only 8% of the patients without PFO mentioned this time relation. Two separate studies have reported this frequency to be 17%<sup>18</sup> and 16%.<sup>17</sup>

TEE is a semi-invasive method with serious side effects in 0.2% of the cases.<sup>24</sup> As a result, we were not able to choose healthy people for controls. Other similar studies also had this limitation. Coagulative evaluations were not complete, and we did not measure some factors such as factor V Leiden. We did not conduct color Doppler sonography of the lower extremities and pelvic veins in the patients with PFO and without PFO.

## Conclusion

In light of the results in the present study and those

reported in the existing literature, we believe that PFO plays a role in the creation of stroke and TIA in young adults. The precise role, however, is not clear yet. The presence of right-to-left shunt at rest and exaggerated motion of the IAS must be considered as risk factors for emboli in patients with PFO. The role of atrial septal aneurysm and PFO size has yet to be fully explored.

Although the present study demonstrated a relation between PFO and stroke and TIA, the appropriate management and follow-up requires further clarification. We need to follow up patients with cryptogenic stroke and TIA in two groups: with PFO and without PFO for stroke and TIA recurrence. If recurrence in the group with PFO is significantly more than that in the group without PFO, therapeutic options for PFO in the prevention of cerebrovascular accidents should be compared.

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