

## Evaluation of patent foramen ovale in young adults with cryptogenic stroke

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### Abstract

**BACKGROUND:** Stroke is a leading cause of death and long-term disability worldwide. Although a minority of ischemic strokes in the community affect younger adults, up to 40% of acute ischemic strokes in young adults are cryptogenic in nature, that is, no cause is determined. Underlying pathologies of stroke of unknown cause are multiple, including patent foramen ovale (PFO). The PFO is the most common defect of atrial septum of the heart. This study evaluated the frequency of PFO in brain stroke with unknown etiology in patients younger than 50 years of age in Kerman.

**METHODS:** This cross-sectional study was done in Shafa Medical Center of Kerman University of Medical Sciences in 2008. For detection of the PFO, we used agitated saline test with transcranial Doppler sonography in brain stroke patients with unknown etiology and also a control group (normal persons).

**RESULTS:** PFO was found in 53% of patients. No significant difference was observed between sexes. The rate in the control group was 20%. Patients with large PFO had 2 or more attacks of stroke. Subjects in the control group did not have large PFO.

**CONCLUSION:** One of the most important underlying causes in young adults with cryptogenic stroke is PFO. It is better to prescribe antiplatelet drugs in patients with the first attack of stroke, but as for patients with recurrent stroke, closure of PFO must be considered.

**Keywords:** Stroke, Young Adults, Patent Foramen Ovale, Agitated Normal Saline Test.

**ARYA Atherosclerosis 2011; 7(2): 74-77.**

*Date of submission:* 5 Dec 2010, *Date of acceptance:* 25 Jul 2011

### Introduction

Stroke is a leading cause of death and long-term disability worldwide. Eighty-five percent of strokes are ischemic, and most of the ischemic strokes occur in persons older than 65 years of age in tandem with the development of atherosclerosis. However, minorities of ischemic strokes in the community affect younger adults.<sup>1</sup>

The risks of recurrent vascular events in young adults who have had ischemic stroke is considerable. In addition, a majority of survivors will have residual emotional, social or physical impairments that hamper employment or lower their quality of life.<sup>2</sup>

Underlying pathologies of stroke of unknown cause include atherosclerosis in brain arteries (although it may not be related to the current stroke). Cardiac findings in a stroke patient may not be related to current stroke (e.g. patent foramen ovale). If the workup for stroke cause is done incompletely or late, it may not find the responsible cause of stroke (e.g.

arterial dissection, mobile intracardiac/luminal thrombus disappeared at the time of examination).<sup>3</sup>

The patent foramen oval (PFO) is the most common defect of atrial septum of the heart.<sup>4</sup> The cause of stroke in a patient with PFO is presumed to be paradoxical embolism, unless there is actual visualization of an entrapped thrombus through the PFO.<sup>5-10</sup> One of the other underlying causes is premature atrial contraction. It has been reported that the frequency of premature atrial contraction is more common in patients with stroke of undetermined etiology in which non-cardiac emboli was thought to be the cause of stroke.<sup>6</sup> It has also been reported that polymorphism in the C5 gene is associated with the risk of ischemic stroke.<sup>7</sup> Using current clinical criteria, 30% of strokes and transient ischemic attacks have been shown to be of undetermined etiology. Gene regulations can cause large vessel atherosclerotic strokes through altering the activity of platelets and monocytes and hemoestasis. Gene regulations are

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effective in cardiac-emboli strokes through neutrophil and modulated immune responses to infectious stimuli.<sup>8</sup>

About 15-20% of cases of brain infarctions occur in patients under the age of 55. Although over 150 causes of stroke have been listed, a thorough evaluation showed that the causes of stroke remain unknown in up to 50-60% of cases in patients younger than 55 years of age<sup>11</sup> and some other studies found this rate to be 40%.<sup>9</sup> In this study we evaluated the frequency of PFO in brain stroke with unknown etiology in patients younger than 50 years old.

### Materials and Methods

This cross-sectional study was done in Shafa Medical Center of Kerman University of Medical Sciences in 2008. All stroke patients less than 50 years old of age that referred to neurology department were evaluated. The patients with one of the following items were excluded: valvular heart diseases, cardiomyopathy, coronary artery disease, anemia and hematologic disorders, cardiac arrhythmia, vasculitis, malignancy, abnormal transcranial Doppler sonography (TCD) of carotids, dissections, contraceptive drugs intake and migraine with aura. The control group has been selected from normal persons (without a history of exclusion criteria and stroke).

The transcranial Doppler sonogram device was joined with DWL 2.5 X2 software box made in Germany. For detection of blood flow in middle cerebral artery (MCA) a 2MHZ probe was used. TCD is a sensitive detector of right-to-left shunt.<sup>12-14</sup>

At first we prepared a questionnaire including age, sex, clinical findings, past history of stroke, results of imaging (brain CT scan or MRI scan) and results of agitated saline contrast test with TCD findings.

While the patients lay on TCD bed, the probe was fixed on the temporal window for MCA blood flow detection. Ten milliliters of contrast fluid (9 milliliters

of normal saline, 0.5 milliliter of patient's blood sample and 0.5 milliliter air) was shaken well until a homogenous fluid was produced. Then, we took an intravenous line by a number 20 angiocatheter on brachial vein. After checking the MCA blood flow, the contrast fluid was injected (for 10 seconds), and the monitor graphs were saved for 10 seconds, and then the test was repeated with Valsalva maneuver (VM). The increase of VM expiratory pressure magnifies the number of microbubbles irrespective of the strain duration. Since the right-to-left shunt classification in PFO is based on the number of microbubbles,<sup>15</sup> if microbubbles were not detected, the test was repeated after 5 minutes. The number of microbubble clicks of monitor graphs was detected. If the number of clicks were more than 10, the PFO was considered large and if they were lower than 10, it was considered small.<sup>16</sup> For all the patients and the control group with PFO, we performed transesophageal echocardiogram without contrast. Only in one of the patients, the PFO wasn't seen.

### Results

This cross-sectional study has been done on 30 cases of stroke under the age of 50 with unknown etiology and 30 normal persons (control group) using agitated normal saline test with TCD.

Table 1 shows the distribution of sex and age of patients, along with the rate of PFO. In the control group the rate of PFO was 20% (6 cases).

There was a significant difference in PFO rate ( $P = 0.01$ ) between the patients and the control group. However, no significant difference was observed in terms of sex and the rate of PFO ( $P = 0.6$ ) among the patients and the control group. Distribution of age showed that most patients were between 25-45 years old. No significant difference existed between the age groups of 26-35 and 36-45 ( $P = 1$ ).

**Table 1.** Distribution of age and sex in patients with and without PFO

		Age groups n(% within Age)				Total
		15-25	26-35	36-45	46-50	
PFO+	female	1(100.0)	4(57.1)	3(50.0)	1(50.0)	9(56.3)
	male	0(0)	3(42.9)	3(50.0)	1(50.0)	7(43.8)
	Total	1(100.0)	7(100.0)	6(100.0)	2(100.0)	16(100.0)
PFO-	female	2(50.0)	3(75.0)	2(66.7)	1(33.3)	8(57.1)
	male	2(50.0)	1(25.0)	1(33.3)	2(66.7)	6(42.9)
	Total	4(100.0)	4(100.0)	3(100.0)	3(100.0)	14(100.0)

Three patients had large PFO but two of them had more than two attacks of stroke. Fourteen patients with PFO had infarction in MCA domain, and two patients had strokes in posterior circulation domain (there isn't a significant difference between two groups).

### Discussion

This study found that the rate of PFO was more than 53% in brain stroke with unknown etiology (cryptogenic), but in control group this rate is 20%. This finding is similar to other reports. There is an association between the presence of PFO and cryptogenic stroke in both old patients and young patients.<sup>17</sup> The most prevalent potential source of cardioembolism in young adults with cryptogenic stroke is PFO, which is detected in more than half of such persons undergoing evaluation.<sup>18-23</sup>

In normal persons, the rate of PFO was 20% which is in agreement with the results of many other reports. In an autopsy study of 965 normal hearts from patients with no history of cardioembolic events, the prevalence of PFO was 27%, and in some reports there was no difference between men and women, regardless of age.<sup>24-26</sup>

In addition, a recent prospective study found a significantly ( $P < 0.02$ ) higher prevalence of PFO in patients with cryptogenic stroke compared with patients with stroke of known cause.<sup>27</sup> In a study, a shunt was found in 20% of stroke patients with known etiology and 50% of unknown etiology.<sup>28</sup>

The rate of PFO in two groups of age (26-35 and 36-45 years) did not reveal any significant differences. Interestingly though, in the lowest age group ( $< 55$  years), the incidence of recurrent stroke or death tended to be lower in patients with a PFO, and it was about equal among people aging 55 to 65. However, subjects with 65-80s of age were 3 times more likely to have a stroke or death if a PFO was present, even after adjustment for other cardiovascular risk factors. As one gets older, he probably has more venous emboli and his right atrial pressure goes up, raising the risk of PFO-mediated embolic events to the point where, in the elderly, that risk may be just as important as the underlying atherosclerotic disease.<sup>29</sup>

A study conducted on general population showed that the PFO, alone or together with atrial septal aneurism, was not associated with an increased stroke risk in this multiethnic cohort.<sup>30</sup>

In our study, the patients with large PFO had more stroke attacks which is similar to other studies. However, a study with a longer period is suggested.

The amount of shunting was the only significant independent variable associated with relapse, i.e. at the end of the follow-up period, the recurrence rate was 0.66% and 8.2% per patient per year in patients with small and large shunt, respectively. In patients with PFO-related stroke, the amount of right-to-left shunt as assessed with TCD is the only independent predictor of relapse. Therefore, PFO sizing is mandatory in patients with PFO.<sup>16</sup> Interestingly, in our study, the PFOs in control group were all small. The association of PFO with other disorders, especially migraine with aura, must be taken into consideration. In a study, the rate of PFO in migraine headache with aura was 40%,<sup>31</sup> but our patients didn't have migraine headaches with aura.

### Conclusion

One of the most important underlying causes in young adults with cryptogenic stroke is PFO. In patients with the first attack of stroke it is better to prescribe antiplatelet drugs, but as for patients with recurrent stroke, closure of PFO must be considered.

### Conflict of Interests

Authors have no conflict of interests.

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