Microembolic Signals in Patients with Cryptogenic Stroke with or without Patent Foramen Ovale

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Background: To evaluate the incidence, frequency, and contributing factors of microembolic signals (MESs) in patients with cryptogenic stroke with or without patent foramen ovale (PFO).

Methods: Transcranial Doppler monitoring for MESs detection was performed for 62 patients with acute cryptogenic stroke with PFO (PFO1) and 34 patients with acute cryptogenic stroke without PFO (PFO2).

Results: The incidence of MESs was not significantly higher in PFO1 patients (17/62, 27.4%) in comparison to PFO2 patients (6/34, 17.6%; odds ratio 1.76, 95% confidence interval 0.62-5.00; P = .327). The frequency of MESs in PFO1 patients was statistically higher than that of PFO2 patients (0.70 ± 1.47 vs 0.23 ± 0.55; P = .026). MESs was presented with higher incidence in a subgroup of patients suffering from both patent foramen ovale and atrial septal aneurysm (P = .044).

Conclusions: The likelihood of PFO as a source of MESs is higher when associated with atrial septal aneurysm. Key Words: Atrial septal aneurysm—microembolic signals—patent foramen ovale—stroke—transcranial Doppler ultrasonography.

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Despite the standard investigations, the etiology of ischemic stroke remains unidentified in about one-third of patients. Patent foramen ovale (PFO) is hemodynamically an insignificant interatrial right-to-left communication found in 24.3% of the randomly sampled subjects during transesophageal echocardiography (TEE). It has been proposed as a possible source of cardioembolism and cryptogenic stroke, but this issue is still a matter of debate. The risk of ischemic stroke recurrence associated with PFO was not increased during prospective studies.1,3 It is estimated that about one-third of PFOs discovered in cryptogenic strokes are incidental findings and are unrelated to stroke.4 There should be some modalities other than simple visualization of PFO during echocardiography that would guide a clinician for proper diagnosis and treatment of a high-risk patient to prevent further stroke. Transcranial Doppler (TCD) sonography and monitoring for spontaneous microembolic signals (MESs) might be one of the available modalities.

Clinically, MESs are silent cerebral emboli that are usually detected during TCD monitoring of the intracranial arteries. Microembolic signals are considered helpful in estimating the persistence of an embolic source after ischemic stroke.5,6 If we consider a PFO as a source of cardioembolism, then we may find more MESs during TCD monitoring.

The aim of this study was to evaluate the incidence, frequency, and contributing factors of MESs in patients with cryptogenic stroke with or without PFO. The current
study was conducted to find “features which may raise the risk of stroke.”

Methods

This case-control study was conducted in Nemazee Hospital, which is affiliated with the Shiraz University of Medical Sciences, Shiraz, Iran, and the study took place between July 2007 and December 2009. Subjects were consecutive patients presenting with single ischemic stroke. Causes of ischemic stroke were categorized into large-artery disease, cardioembolism, small-vessel disease, other determined cause of stroke, and undetermined cause according to Causative Classification of ischemic Stroke - Trial of Org 10172 in Acute Stroke Treatment (CCS-TOAST) classification. Those patients classified as Stroke - Trial of Org 10172 in Acute Stroke Treatment cause according to Causative Classification of ischemic consecutive patients presenting with single ischemic stroke. between July 2007 and December 2009. Subjects were recruited. Inclusion criteria were none severe stroke (modified Rankin scale score ≤3) within 30 days of enrollment and an age of more than 18 years. This project was approved by the Ethics Committee of Shiraz University of Medical Sciences (no. 88-4641). Written informed consents were obtained from all the participants or their first-degree families.

Exclusion criteria were the presence of any determined cause for ischemic stroke. These included evident large-artery atherosclerosis as >50% stenosis or occlusion of major brain artery or the cortical artery branch; unequivocal cardiac sources of embolism as chronic or paroxysmal atrial fibrillation, mitral stenosis, mechanical heart valve, endocarditis, intracardiac clot, or vegetation, myocardial infarction within 3 months, dilated cardiomyopathy; and ejection fraction <30%; small-vessel disease as cortical, cerebellar, brain stem, or subcortical infarct <1.5 cm; other determined cause of stroke as any known vasculitis, any known thrombophilic disease, any infectious vasculopathy, arterial dissection, Moya–Moya disease, radiation-induced vasculopathy, fibromuscular dysplasia, sickle cell disease, neurofibromatosis, reversible cerebral vasoconstriction syndrome, vasospasm after subarachnoid hemorrhage, and cerebral sinus venous thrombosis. Those patients with 2 or more major causes of stroke for which a primary cause could not be determined were also excluded. In addition, patients without a proper temporal window for TCD monitoring or without compliance for echocardiography or TCD monitoring were excluded.

Age and sex of the patients and the presence of any vascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, previous cerebral ischemic event, and cigarette smoking in the past 10 years, were recorded.

Hypertension was defined as a blood pressure ≥140/90 mm Hg measured before an ischemic event by a medical professional. Symptoms of diabetes plus random blood glucose concentration >200 mg/dL or fasting plasma glucose >126 mg/dL measured before an ischemic event were defined as diabetes mellitus. Hyperlipidemia was diagnosed as fasting plasma level of triglyceride >200 mg/dL and/or fasting low-density lipoprotein level >130 mg/dL before an ischemic event.

Brain computed tomography scan and magnetic resonance imaging, routine laboratory tests, electrocardiograms, color duplex sonography of extracranial arteries, TCD sonography of intracranial arteries, and TEE was conducted for the patients on admission.

TEE with saline injection was conducted according to a routine protocol using a Vivid 3 Echo machine (GE Medical Dystems, Oslo, Norway). PFO was defined as the appearance of at least 3 bubbles in the left atrium during 5 cardiac cycles after opacification of the right atrium with contrast bubbles whether spontaneously or after Val-salva maneuver. Atrial septal aneurysm (ASA) was defined as a deviation of the interatrial septum to the left, right, or bidirectionally >10 mm at any time during the cardiac cycle with a diameter of the base of aneurysmal portion of at least 15 mm.

According to the results of the above investigations, patients with cryptogenic stroke had been recruited and underwent TCD monitoring. The patients were divided into 2 groups of case and control patients. The cases were stroke patients with PFO during TEE (PFO). The controls were stroke patients without PFO (PFO'). For better classification, they were divided into 4 groups: those with PFO and ASA (PFO+/ASA+), isolated PFO (PFO+/ASA+), isolated ASA (PFO-/ASA+), and with normal interatrial septum (PFO-/ASA-).

A Sunray TCD ultrasound device machine (version FD-T98II; Guangzhou Doppler Electronic Technologies, Guangzhou, China) was used for TCD monitoring. The patients were instructed to lie in the supine position. Two 2-MHz transducers were fixed on the temporal windows using a helmet. Both middle cerebral arteries’ main stems were insonated simultaneously for 60 minutes. The device was set to a small sample volume of 10 mm in length and minimum possible gain to provide an optimal setting for MES discrimination from the background spectrum. The definition and detection of MES was based on the International Consensus Group on microembolus detection criteria: the random appearance of unidirectional, short duration (<0.3 sec), high-intensity signal (>9 dB above the background) with typical visible and audible (click, chirp, and whistle) properties. One investigator performed TCD monitorings and analyzed the waveform online. He noted the exact number and position of MESs. The other investigator reviewed the recordings offline. Only signals recognized by both investigators in 2 successive studies were detected as MESs. Both investigators were blinded about the presence or absence of PFO and ASA.

Statistical analyses were performed with SPSS software (version 15.0; SPSS Inc, Chicago, IL). The results are
expressed as percentages and absolute frequencies where appropriate. The Chi-square and \( t \) tests were used for comparison of the variables between the groups. \( P < .05 \) was considered statistically significant.

**Results**

Considering all inclusion and exclusion criteria, 96 patients were recruited. Sixty-two patients had PFO (PFO\(^+\), considered cases) and 34 did not have this cardiac septal abnormality (PFO\(^-\), considered controls). Twenty-three patients had both PFO and ASA, 39 patients had isolated PFO, 9 patients had isolated ASA, and 25 patients had normal interatrial septum.

The age and sex distributions and presence of hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, and cigarette smoking had no significant difference in the case group as compared to the control group (Table 1). ASA was present in 37.1% (23) of the PFO\(^+\) patients and 26.5% (9) of the PFO\(^-\) patients (\( P = .367 \)).

The incidence and frequency of MESs in PFO\(^+\) patients was not statistically associated with age, sex, hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, or cigarette smoking (\( P > .05 \)). The incidence and frequency of MESs in PFO\(^+\) patients was not associated with these vascular risk factors (\( P > .05 \)) save for hypertension, in which the frequency of MESs was significantly higher in patients with hypertension (0.43 ± 0.72 vs. 0.05 ± 0.23; \( P = .043 \)).

MESs were found in 27.4% (17) of the PFO\(^+\) patients and 17.6% (6) of the PFO\(^-\) patients (odds ratio [OR] 1.76, 95% confidence interval [CI] 0.62-5.00, \( P = .327 \)). The mean number of MESs per hour in PFO\(^+\) patients was statistically higher than that of PFO\(^-\) patients (0.70 ± 1.47 vs 0.23 ± 0.55; \( P = .026 \)).

In PFO\(^+\)/ASA\(^+\) patients, the incidence of MES was significantly higher compared to other patients (\( P = .044 \)), compared to the subgroup of patients with PFO\(^+\)/ASA\(^-\) (OR 5.04, 95% CI 1.52-16.64; \( P = .008 \)), and compared to those without PFO and ASA (OR 3.66, 95% CI 1.02-13.14; \( P = .041 \)). The incidence of MES was higher in PFO\(^+\)/ASA\(^+\) patients compared to PFO\(^-\)/ASA\(^+\) patients; however, this difference was not statistically significant (OR 7.33, 95% CI 0.78-68.47; \( P = .103 \)). The incidence of MES among different patient subgroups is shown in Figure 1. The mean number of MESs per hour in patients with PFO\(^+\)/ASA\(^+\) was 1.30 ± 1.98 compared to 0.36 ± 0.93 in patients with PFO\(^+\)/ASA\(^-\) (\( P = .002 \)), 0.22 ± 0.67 in patients with PFO\(^-\)/ASA\(^+\) (\( P = .023 \)), and 0.21 ± 0.51 in normal PFO\(^-\)/ASA\(^-\) (\( P = .022 \)).

**Discussion**

Although PFO was not associated with a higher incidence of MESs in patients with cryptogenic stroke, when PFO co-occurred with ASA, MESs presented with higher incidence and frequency. In this subgroup of patients, MES was present in approximately one half of the patients and the incidence of MES was significantly higher than that in isolated PFO and normal interatrial septum. The likelihood of PFO as a source of MES was higher when associated with ASA.

To the best of our knowledge, the association of MES with PFO was evaluated in only 1 study, and no study was conducted to evaluate the association of MES with ASA. In the mentioned study, the presence of MES was evaluated in 14 patients with PFO, in whom MES presented among 21.4% of their patients, more than what we observed in patients with isolated PFO (15%) and less than in patients with PFO and ASA (47%).

Different studies have shown the predictive value of the incidence of MES for further stroke in patients with ischemic stroke and symptomatic carotid stenosis. No relation for the frequency of MES was found. In addition, MES-positive asymptomatic carotid stenosis did not have a higher risk of cerebrovascular events. Considering the results of these studies, the higher incidence of MES in patients with cryptogenic stroke with PFO and ASA shows a higher risk of stroke recurrence in this subgroup of patients. These patients may need more vigorous treatments. Our finding is consistent with previous studies, which found a substantial risk for recurrent stroke in patients with both PFO and ASA. In a meta-analysis of case-controlled studies, the association of PFO and ASA yielded a lower probability of being an incidental finding. However, in the PFO in cryptogenic stroke

| Table 1. Comparison of vascular risk factors in poststroke patients with patent foramen ovale and without patent foramen ovale |
|------------------|------------------|------------------|
|                   | With PFO         | Without PFO      | \( P \) value |
| Age, y (mean ± SD)| 59.5 ± 14.1      | 64.4 ± 12.7      | .092          |
| Male              | 33 (53.2%)       | 22 (64.87)       | .291          |
| Hypertension      | 25 (40.3%)       | 16 (47.1%)       | .667          |
| Diabetes mellitus | 7 (11.3%)        | 8 (23.5%)        | .145          |
| Hyperlipidemia    | 14 (22.6%)       | 7 (20.6%)        | .821          |
| Ischemic heart disease | 8 (12.9%)     | 8 (23.5%)        | .252          |
| Cigarette smoking | 20 (32.3%)       | 12 (35.3%)       | .823          |

Abbreviations: PFO, patent foramen ovale; SD, standard deviation.
No significant difference in the time to stroke recurrence or death among patients with isolated PFO or those with both PFO and ASA were observed.16

There is controversy about the association of PFO in cryptogenic stroke with further stroke. While the association between PFO and cryptogenic stroke had been established,17 the evidence is against the increased risk of subsequent stroke associated with PFO. A recently published metaanalysis revealed that in patients with cryptogenic stroke, the risk of recurrence is not significantly different in those with or without PFO.18 Unlike other definite sources of cardioembolism, such as prosthetic heart valve and atrial fibrillation, there are no significant differences in the rate of stroke recurrence observed between patients treated with aspirin or warfarin.16,19 Because PFO is a common congenital anomaly in the general population,1 it may be found incidentally in cryptogenic strokes without any clinical implications.4 Differentiation between innocent and pathogenic PFO and that of those with increased risk of further risk is still a dilemma in approaching a cryptographic stroke with PFO. MESs as a predictor of further stroke may be one of the available solutions to this problem. The presence of MESs in the acute phase of stroke was significantly higher in patients with embolic etiology for stroke compared to those of nonembolic strokes.20 The presence of MESs in the post-stroke phase in a patient with cryptographic stroke and PFO may point to a pathogenic PFO for ischemic stroke. It had been found that the prevalence of PFO in younger stroke patients is four-fold that of older patients.17 We did not find any association between MES and age of the patients. In addition, the incidence of MES was not associated with any vascular risk factors for stroke. We may propose that selection of patients for TCD monitoring and MES detection is not dependent on the patients' age or any vascular risk factors.

This study had some limitations. The predictive value of MES for further stroke in patients with PFO has not been evaluated yet in a prospective study. Additional studies are required to confirm whether patients with PFO and ASA who had MES during TCD monitoring would benefit from anticoagulation or device closure of PFO. The absence of temporal window and incompliance during TCD monitoring had led to exclusion of about 25% of patients with cryptographic stroke. This may have affected the results. The smaller sample size of patients with isolated ASA was related to the lower prevalence of this cardiac anomaly compared to PFO and its co-occurrence with PFO in most cases. Therefore, these data were insufficient to help draw a conclusion about isolated ASA. Additional studies with larger sample sizes in prospective fashion are recommended.

In conclusion, our study is the first study that revealed a higher incidence of MES in cryptographic strokes with combined PFO and ASA compared to other isolated interatrial septal abnormalities and normal interatrial septum. Performance of TCD monitoring in patients with cryptographic stroke who suffer from both PFO and ASA may distinguish patients with higher risk for further stroke.

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References


