

Clinical and trans-esophageal echocardiographic evaluation of patent foramen ovale in young Iraqi patients with ischemic stroke

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Abstract

Background: Patent foramen ovale (PFO) has been long identified as a potential risk factor for stroke, but the mechanism or mechanisms of PFO-associated stroke remain unsettled and controversial till now.

Aim: To evaluate possible differences in stroke risk factors and stroke patterns between patients with and without PFO using trans-esophageal echocardiographic study that may give clues to the mechanism of PFO-associated stroke that is mainly seen in young people.

Methods: This short-term cross-sectional observational study involved 95 consecutive young cryptogenic stroke patients. The study was conducted at the Baghdad Teaching Hospital from January 2003 to February 2006. The presence of PFO was assessed by trans-esophageal echocardiography (TEE).

Results: Of the 95 stroke patients, 32 (33.68%) had PFO. Patients with PFO were younger (OR, 0.95; 95% CI, 0.93 to 0.97) and less likely to have traditional risk factors such as hypertension (OR, 0.49; 95% CI, 0.28 to 0.85), hypercholesterolemia (OR, 0.56; 95% CI, 0.34 to 0.93), or current smoking (OR, 0.67; 95% CI, 0.47 to 0.97). Features suggestive of paradoxical embolism, such as Valsalva-provoking activities (by careful history taking) or deep vein thrombosis were not more frequent in patients with PFO.

Conclusions: Differences in stroke risk factors and stroke patterns suggest that different stroke mechanisms occur in patients with and without PFO.

Keywords: patent foramen ovale; embolic stroke; trans-esophageal echocardiography.

Introduction

Patent foramen ovale (PFO) has been identified as potential risk factors for stroke and many studies had shown that severe shunting and wide opening of PFO are risk factors for severe and recurrent cerebro-vascular events. PFO is an anatomical interatrial communication with potential for right-to-left shunt. Foramen ovale has been known since the time of Galen. In 1564, Leonardi Botali, an Italian surgeon, was the first to describe the presence of foramen ovale at birth. However, the function of foramen ovale in utero was not known at that time. In 1877, Cohnheim described paradoxical embolism in relation to patent foramen ovale [1-6]. Its limited importance lies in the propensity for either left-to-right shunting or right to-left shunting due to a grossly incompetent valve of the fossa ovalis. Shunting can occur through dilation of the valve orifice secondary to either right atrial or left atrial enlargement. "Paradoxical embolism" (venous thrombus which migrates and enters the systemic circulation through a patent foramen ovale) is possible during specific clinical scenarios [7-9].

Patients & Methods

This observational study was conducted at the Baghdad Teaching Hospital general

medical and neurology wards. Patients were consecutively included between January 2003 to February 2006; there was an omitted period from March 15 to June 1, 2003 because of the US-lead war against Iraq). Because of the current and limited circumstances in our echo lab after the War in Baghdad Teaching Hospital, many patients underwent their trans-esophageal echo study in Ibn Al-Baitar Hospital and Al-Khadhimiya Teaching Hospital. The echo study was performed and interpreted by cardiologists and trainees of the Iraqi board of internal medicine and the Iraqi board of cardiology.

Brain CT scans and MRIs were done in the Surgical Specialties Hospital in the Medical City Complex, Neurosurgery Hospital, Al-Yarmook Teaching Hospital, and Al-Khadhimiya Teaching Hospital and were interpreted by radiologists. The clinical and neurological examinations were carried out by trainees of the Iraqi board of neurology and the Iraqi board of internal medicine at the Baghdad Teaching Hospital.

Inclusion criteria and initial workup:

Inclusion criteria were as follows: age between 18 and 55 years; recent (3 months) ischemic stroke (neurological deficit lasting >24 hours); no definite cause of stroke after somewhat "an extensive" and standardized etiological

workup (according to our available lab investigations in Baghdad), including cerebral CT scan (n=95), MRI (n=32), routine blood tests and some specific tests (the later did not include protein S, protein C, and anti-thrombin III, which are not available) and anti-phospholipid antibodies; 12-lead ECG and echocardiography (n=95); and 1 of the following arterial investigations (within 1 month of stroke onset): MRI angiography (n=7), or neck ultrasonography for carotid artery stenosis (n=95). A 24-hour ECG recording was performed in selected patients (n=32 with PFO) between days 7 and 21 after stroke onset. Twenty-four-hour ECG monitoring was performed after the acute phase of stroke to exclude arrhythmias secondary to stroke.

Clinical data:

The following information was systematically recorded:

- (1) Baseline characteristics and traditional risk factors of stroke (table 1).
- (2) Past vascular events, such as stroke, deep venous thrombosis, or pulmonary embolism.
- (3) History of migraine according to International Headache Society criteria [10].

(4) Palpitations preceding or accompanying stroke onset.

(5) Neurological features reported as suggestive of cardiogenic embolism [11,12], such as abrupt, non-progressive onset defined as no deficit on waking from sleep, peak deficit within the first 10 minutes, no subsequent deterioration during the first 24 hours, diminished level of consciousness at onset, cortical deficits, including Wernicke's aphasia, isolated hemianopsia, hemineglect, and apraxia.

(6) Features suggesting paradoxical embolism, such as the presence of deep venous thrombosis or pulmonary embolism, Valsalva-provoking activity within the 30 minutes preceding stroke onset (sporting effort, straining at stool, intercourse, lifting a heavy weight, getting up, laughing, and coughing)[13], and circumstances predisposing to deep venous thrombosis before stroke onset, such as immobilization, anesthesia, surgery, or pregnancy [14].

Brain and vascular imaging findings:

The following brain and vascular imaging features were analyzed: Stroke arterial territory [15-17];

imaging features of previous stroke; neuro-imaging data suggestive of cardiogenic embolism [18-20] such as hemorrhagic infarct on neuroimaging performed within 2 weeks of stroke onset [20], superficial infarct, infarct larger than one half of the cerebral hemisphere, involvement of specific (table 2) or multiple arterial territories [21].

Echocardiography:

The presence of PFO and ASA was assessed by trans-esophageal echocardiography. Unfortunately very few patients (n=2) underwent a contrast study using an agitated saline performed at rest and during provocative maneuvers (Valsalva and cough test) because many operators did not use this contrast during the echocardiographic evaluation and hence we did not assess the degree of the shunt (mild, moderate or severe).

Statistical Analysis:

Clinical data and brain and vascular imaging findings were compared between patients with and without PFO. Comparisons between these 2 groups were performed by a 2-test, Fisher's exact test, or *t*-test for unpaired data whenever applicable.

Factors independently associated with PFO were identified by logistic regression analysis. ORs with 95% CIs were calculated.

Results

This study included 95 consecutive patients. Of these, 32 patients (33.68%) had PFO and 12 (12.6%) had ASA. PFO was strongly associated with ASA: 10 of the 32 patients with PFO (31.2%) also had ASA compared with those without PFO (3.1%; $P < 0.0001$).

Patients' characteristics and stroke patterns:

Baseline characteristics and risk factors of stroke, according to the presence of a PFO, are shown in Table 1. Patients with PFO were younger and less likely to have traditional risk factors of stroke than those with no PFO. In logistic regression analysis (with age, sex, stroke risk factors, and ASA as independent variables), age (OR, 0.95; 95% CI, 0.93 to 0.97), hypertension (OR, 0.49; 95% CI, 0.28 to 0.85), hypercholesterolemia (OR, 0.56; 95% CI, 0.34 to 0.93), and current smoking (OR, 0.67; 95% CI, 0.47 to 0.97) were inversely associated with PFO, whereas ASA (OR, 7.4; 95% CI, 3.6 to 15.2) was positively associated with PFO.

Table 1: Demographic risk factors for stroke in patients with and without PFO.

	No PFO (n=63)	PFO (n=32)	P-value
Age (mean),year	44.5	40.1	<0.0001
Male sex, %	63.4	53.1	0.02
Risk factors			
-hypertension,%*	25.3	9.3	<0.0001
-diabetes mellitus,%*	4.7	3.0	0.2
-hyper-cholesterolemia,%*	23.8	10.9	<0.0001
-current smoking*	55.7	40.6	0.05
-alcohol**	22.2	31.2	0.01
-current use of oral contraceptive pills (in females), %	40.3	51.6	0.08
Body mass index, >30 Kg/m^{2***}, %	30.1	18.7	0.003
Prior stroke,%	4.7	3.1	0.5

n=95

*known before stroke

**more than 3 standard drinks per day. Kenneth J, Ascherio A, Mittleman M, *et al. Alcohol and Risk for Ischemic Stroke: The Role of Drinking Patterns and Usual Beverage.* Ann Int Med 2005; 142:11-9.

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Table 2 shows the characteristics of stroke. Overall, no difference was found regarding arterial territories. Neuroimaging features of previous stroke were

less frequent in patients with PFO, but this association was not significant after adjustment for age and risk factors for stroke.

Table 2: Stroke patterns in patients with and without PFO.

	No PFO% (n=63)	PFO% (n=32)	P-value
Clinical features			
abrupt onset	55.5	62.5	0.006
impairment of consciousness at onset	9.5	12.5	0.3
cortical signs	22.2	31.2	0.004
Brain and vascular imaging features			
-circulation			0.4
anterior	61.9	53.1	
posterior	36.5	43.7	
anterior and posterior	1.5	3.1	
-small deep infarcts	9.5	9.3	0.7
-features of previous stroke	14.2	12.5	0.01
-hemorrhagic infarction	11.1	12.5	0.8
-size >1/2 hemisphere	4.7	6.2	0.1
-superficial infarct	52.3	56.2	0.4
-MCA posterior division	12.6	12.5	0.9
-superficial PCA	9.5	6.2	0.6
-multiple recent infarcts	null	3.1	0.2
-superior cerebellar artery	1.5	9.3	0.001

MCA=middle cerebral artery, PCA=posterior cerebellar artery

Mechanism of PFO-associated stroke:

Clinical and imaging features suggestive of cardiogenic embolism did not differ significantly between groups, except for a higher frequency of cortical signs and of infarcts in the superior cerebellar artery territory in the PFO group. Features consistent with the diagnosis of

paradoxical embolism were not found more frequently in patients with PFO than in patients without PFO, except for a higher frequency of circumstances predisposing to deep venous thrombosis (Table 3).

Table 3: Arguments suggesting paradoxical embolism.

	No PFO% (n=63)	PFO% (n=32)	P-value
Valsalva-provoking activity within 30 minutes preceding stroke onset*	9.5	12.5	0.2
History of DVT or pulmonary embolism	3.1	3.1	0.2
Circumstances predisposing to DVT before stroke onset**	1.5	6.2	0.05

DVT=deep venous thrombosis, n=95

*sporting effort, straining at stool, intercourse, lifting heavy weight, getting up, laughing, and coughing

**immobilization, anesthesia, surgery, and pregnancy

Of the 32 patients with PFO, 17 (53.1%) had a search for latent deep venous thrombosis or pulmonary embolism within 4 weeks after stroke onset (43.7% within 8 days). Investigations consisted of Doppler ultrasonography of the lower limbs (n=32). A latent deep venous thrombosis was found in 2 patients (6.2%) 4 to 12 days after stroke onset. Palpitations preceding or accompanying stroke onset were rare and even less common in patients with PFO (3.1% versus 7.9% in those without PFO; P=0.06). Twenty four-hour ECG recording did not reveal emboligenic arrhythmias in patients with PFO in whom it was performed.

Discussion:

We selected patients younger than 55 years of age because the higher prevalence of large-vessel atherosclerosis or small-artery disease in the elderly makes the diagnosis of cryptogenic stroke less frequent than in the young. In addition, the association of PFO and cryptogenic stroke has been consistently reported in this age group, whereas this association in those >55 years of age remains unconfirmed [6]. The first finding of this study is that cryptogenic stroke patients with PFO were younger and less likely to have traditional risk factors for stroke than patients without PFO and this may suggest different stroke mechanisms in patients with and without PFO.

Some features suggestive of cardiogenic embolism were more frequent in the PFO group, which also suggests different stroke

mechanisms in patients with and without PFO. These features, however, have a limited positive or negative predictive value for the diagnosis of cardioembolism [21]. On the whole, features suggesting paradoxical embolism were not more frequent in patients with PFO than in those without PFO, suggesting that paradoxical embolism might not be the prevalent mechanism of PFO-associated stroke [22]. These features, however, may be insufficient or inaccurate and therefore not useful in clinical practice. The frequency of latent deep venous thrombosis in stroke patients with PFO was not an objective in this study, and the search for deep venous thrombosis was done in patients with a suggestive clinical picture. It was performed in few patients with PFO by use of Doppler study. Indeed, the source of emboli may remain undetected because of its location or the size of the thrombus [22-24]. Venous thrombi may disappear either spontaneously or after anticoagulation before investigations are performed, so it was searched for in few patients. Finally, venous thrombosis may be a mere consequence of immobilization resulting from stroke rather than a cause of stroke. The role of a hypercoagulable state in the pathophysiology of PFO-associated stroke cannot be evaluated from this study because patients with a definite

coagulopathy were not included in the study.

This study does not provide argument for transient arrhythmia as a mechanism of PFO-associated stroke. Palpitations preceding or accompanying stroke onset were rare and 24-hour ECG recording did not reveal emboligenic arrhythmias. It should be stressed, however, that arrhythmias are often clinically silent [25] and that a single 24-hour Holter monitoring is not the optimal method to detect potentially more spaced-out episodes of transient arrhythmias [26].

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