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Original article

Prevalence of patent foramen ovale in subjects with obstructive sleep apnea: a transcranial Doppler ultrasound study

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Abstract

Background: Under particular conditions a patent foramen ovale (PFO) can potentially give rise to ischemic stroke by means of paradoxic embolization. In obstructive sleep apnea syndrome (OSAS) right to left shunting (RLSh) can occur through PFO during periods of nocturnal apnea. Our study aimed to evaluate the prevalence of PFO diagnosed by means of transcranial Doppler (TcD) in subjects with OSAS.

Methods: Seventy-eight consecutive subjects with OSAS (mean age 53 ± 12 years) and 89 normal controls (mean age 48 ± 9 years) underwent TcD with intravenous application of agitated physiological saline solution. The test was performed on patients at rest and during Valsalva maneuver.

Results: PFO was present in 21 out of 78 patients with OSA (27%) and in 13 out of 89 control patients (15%). Seventeen out of 21 patients with OSA showed PFO only during Valsalva maneuver (85%) with respect to 12 out of 13 subjects of the control group (92%). Prevalence of PFO in OSAS was statistically different with respect to the control group ($P < 0.05$). However, no statistically significant differences could be found for the prevalence of provocative-only shunting PFO with respect to already at rest shunting PFO in patients with OSAS with respect to the control group.

Conclusions: Prevalence of PFO in subjects with OSA is significantly higher than in normal controls. The shunt is frequently present only during Valsalva maneuver.

Keywords: Intracardiac shunting; Obstructive sleep apnea; Patent foramen ovale; Transcranial Doppler

1. Introduction

Patent foramen ovale (PFO) is the most frequent of interatrial communications. In studies with autopsy-identified PFO, prevalence ranges from 10 to 34% with a decreasing trend of prevalence in the elderly [1–3]. Transesophageal echocardiography (TEE) confirmed this range of prevalence in the normal population [4–7].

In subjects with ischemic stroke, prevalence of PFO is approximately 40–54% [8–10], reaching 47–77% [11–15] if only patients with cryptogenic ischemic stroke are studied. It is thought that a PFO can potentially give rise to ischemic stroke by means of paradoxic embolization [13,16,17], and it is seen as a dominant cause of stroke in young people.

The mechanism consists of the passage of venous clots through the PFO into arterial circulation, thus favoring cerebral embolism. Because of its valve-like nature, PFO may allow right to left shunting (RLSh) between the right and the left atria during the cardiac cycle as a result of a transient, instantaneous pressure gradient [18,19]. When RLSh occurs in basal conditions with normal breath, PFO will sometimes be defined as 'at rest shunting'. However, the maximum degree of shunting is usually reached during provocative maneuvers (e.g. Valsalva maneuver), which increase right cardiac chamber pressure (i.e. 'provocative-only shunting' PFO). Right atrial pressure increase is chronically present in subjects with pulmonary hypertension [20,21]. But such a condition of higher right compared to

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left atrial pressure can also occur during everyday events such as coughing, sport efforts, heavy weight lifting, breath instrument playing similar to the provocative Valsalva maneuver. Furthermore, a recent study by our group showed that RLSh also occurs in subjects with obstructive sleep apnea syndrome (OSAS) during periods of nocturnal apnea, if the apnea length is longer than 17 s [22]. OSAS, in particular, is not a rare condition in the general population; its prevalence ranges from 0.3 to 8.5%, depending on differences in definitions, age, sex and other characteristics of the population surveyed [23,24].

Only one previous study evaluated the prevalence of PFO in subjects with OSAS by means of TEE. This group found an increased prevalence of PFO in subjects with OSAS (69 vs. 17% in the control sample), but sample size was small [25].

Nowadays, transcranial Doppler (TcD) with contrast medium has been proven to have the same sensitivity and specificity as TEE with contrast medium, a semi-invasive technique, until recently the only reliable tool for the diagnosis of PFO. Furthermore, it has been demonstrated that this new technique is better tolerated by patients, permitting a better execution of the Valsalva maneuver, which is considered the gold standard for the diagnosis of provocative-only shunt [14,26–29].

The aim of this study is to evaluate by TcD in a large sample the prevalence of RLSh in subjects with OSAS.

2. Patients and methods

2.1. Study sample

We studied by clinical assessment and overnight sleep studies 78 consecutive subjects with documented OSAS (mean age 53 ± 12), 66 males and 12 females. The control group was composed of 89 healthy control subjects without history of sleep apnea or snoring (mean age 48 ± 9), 45 males and 44 females.

2.2. Including and excluding criteria

For both groups, subjects were included in the study only if they had neither prior myocardial infarction, unstable angina, decompensated congestive heart failure, nor history of migraine, Transient Ischemic Attack (TIA) or stroke, active infectious pulmonary process, prior pulmonary embolism or pulmonary infarction. Furthermore, subjects were also excluded from both groups if either stenosis of extracranial arteries or blood flow velocity alterations of intracranial arteries were assessed by means of bilateral Doppler sonography.

2.3. Diagnosis of OSAS

The presence of OSAS was assessed by means of standard nocturnal polysomnography, which included electroencephalogram, electro-oculograms, submental and anterior tibial electromyograms, measurements of oro-nasal airflow, chest and abdominal excursions, oxyhemoglobin saturation (finger pulse oximetry) and single-lead electrocardiogram. Polysomnograms were scored following the standard sleep staging criteria.

Respiratory events, scored manually by a single expert, were defined as apnea when the amplitude of the thermocouple signal decreased completely or to >80% of baseline airflow amplitude. A qualifying event lasted at least 10 s. The criterion to define hypopnea was a clear reduction in the amplitude of the thermocouple signal to below 50% of the amplitude of 'baseline' breathing for more than 10 s. All respiratory events were scored only for the characteristics of the signals obtained from the thermocouple and the chest- and abdominal belts, independently to the SaO_2 level. The number of apneas and hypopneas per hour (apnea–hypopnea index, AHI) was computed. All subjects with an AHI > 10 (mean 52 ± 25) were included in the study.

All night SaO_2 was sampled every 2 s and later analyzed for baseline SaO_2 during wakefulness, minimal saturation of SaO_2 dip, and sleep time spent below 90, 80 and 70% of SaO_2.

2.4. PFO assessment

In all subjects the presence of RLSh was evaluated by means of TcD (Multidop DWL, Sipplingen, Germany) with injection of contrast medium. The machine employed a 64-point fast Fourier transform analysis and used a graded color scale to display the intensity of the Doppler signal received. Every online examination was recorded onto hard disk and analyzed off-line immediately after every session.

The basic principle of this technique is that a gaseous contrast medium injected into a peripheral vein is expired at the pulmonary level in physiologic condition. In the presence of a PFO, microbubbles pass from the right to the left circulation during the cardiac cycle and enter the systemic circulation; the microbubbles can thus be recorded as microembolic signals by TcD in the middle cerebral artery. Performance criteria of contrast TcD for the diagnosis of RLsh followed those recommended in the meeting report of the consensus conference [28,29] held in Venice in April 1999 at the Fourth Meeting of the European Society of Neurosonology and Cerebral Hemodynamics:

> Patients assumed the supine position, with the arm horizontal. Blood flow on middle cerebral artery was recorded bilaterally and simultaneously to increase sensitivity [30] by two transcranial pulsed-wave 2 MHz ultrasound probes fixed at the patient's head at the level of the temporal bone window. An intravenous Daflon catheter (#18) was inserted into the cubital vein and was connected to a 250 ml bottle of physiologic solution by means of a flexible tube to maintain venous access for the

whole duration of TcD. Two 20 ml syringes were prepared: one containing 9 ml of physiologic solution and the other containing 1 ml of air. By means of a three-way stopcock, the contents of both syringes were rapidly mixed until a homogeneous solution was obtained (i.e. the contrast medium). The contrast medium was rapidly injected (<5 s) in bolus form with the patient at rest and physiological respiration, session A. The examination was subsequently repeated with maximal magnitude Valsalva maneuver, session B. In session B, 5 s after injection of contrast medium, the examiner ordered the patient to begin Valsalva maneuver. The overall Valsalva maneuver duration was of 10 s. The Valsalva maneuver was trained with the patients before the procedure and the efficacy of Valsalva maneuver in magnitude and consistence for the 10 s was ascertained beforehand through the reduction by at least on third of the systolic flow velocity on middle cerebral artery.

The criterion for the presence of RLSh was the recording of at least one clear microembolic signal, excluding any kind of artifactual origin of the signal, within 20 s from injection [29]. This time frame was considered evidence of RLsh at atrial level [30,31], permitting diagnosis of PFO. If a test was negative or of dubious positivity (one microembolic signal) during the Valsalva maneuver (session B), this session was repeated.

The number of recorded microembolic signals, counted by the software included in the TcD (Multidop DWL, Sipplingen, Germany), was collected separately for every session. The characteristic high intensity transient signal (HITS)—a visible and audible (click, chirp, whistle) signal of short duration (<0.1 s) and high intensity (>3–10 dB) within the Doppler flow spectrum (Fig. 1)—enables to determine the latency of the first microembolic signal [28–31]. Latency was defined as the time passed from the start of injection to the recording of the first microembolic signal.

Microembolic signals in basal conditions (session A) accounted for at-rest shunting PFO. Provocative-only shunting PFO was indicated on the basis of microembolic signals only in the Valsalva session (session B).

Magnitude of RLSh was classified as small (<10 microembolic signals), middle (≥10 < 20 microembolic signals), or large (≥20 microembolic signals); large RLSh was divided into ‘ ≥ 20 microembolic signals but no curtain pattern’ and ‘ ≥ 20 microembolic signals with curtain pattern’ [28].

2.5. Statistical analysis

Prevalence of PFO in patients with OSAS was compared with prevalence of PFO in the control group, as was distribution of provocative-only shunting PFO compared to at-rest shunting PFO within each group. We also aimed to evaluate differences in the distribution of the different

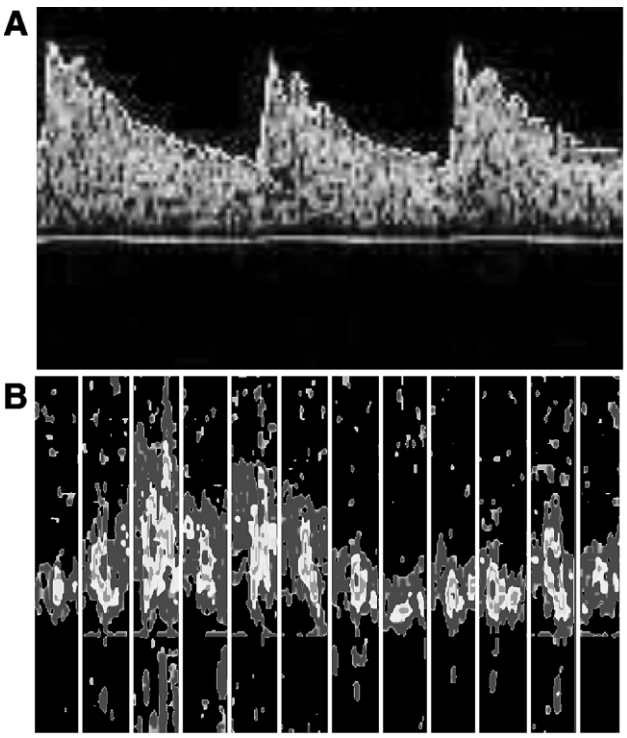

Fig. 1. Examples of TcD spectrum of middle cerebral artery in one single subject in basal condition (A), without RLsh, and during Valsalva maneuver with RLsh (B). In B, the function for automatic emboli count is activated and every single window is corresponding to a time period of 1 s with grasps of microembolic signals (white pixels of the spectrum).

magnitudes of provocative-only shunting PFO. Differences of prevalence between the OSAS sample and the control group were evaluated by means of χ^2 test. A P value <0.05 was considered statistically significant. The hypothesis that statistically significant associations could exist between the occurrence of RLSh and clinical parameters (i.e. age, body mass index, AHI, years of apneic history, mean apnea length, baseline SaO_2 in wakefulness, nadir of SaO_2 during sleep and sleep time in percentage with SaO_2 below 90, 80 and 70%) were evaluated by stepwise logistic regression. All computations were performed by using the SAS package (software version 6, SAS Inc) [32].

3. Results

RLSh was detected in basal and/or during Valsalva maneuver in 21 patients with OSAS (27%) out of 78 and in 13 of those in the control group (15%) out of 89 ($P < 0.05$). Seventeen patients out of 21 with OSAS showed RLSh only during Valsalva maneuver (85%), compared to 12 subjects (92%) out of 13 in the control group (Table 1). Four patients out of 21 with OSAS, and only one subject out of 13 in the control group, also showed RLSh at basal condition. However, these differences were not statistically significant. We found no statistically significant differences in the prevalence of provocative-only shunting PFO or in the

Table 1
Prevalence of PFO in the OSAS vs. control sample

	RLSh magnitude	Total		P	RLSh in basal condition		RLSh during Valsalva maneuver		P
		OSAS ($n = 78$)	Controls ($n = 89$)		OSAS ($n = 78$)	Controls ($n = 89$)	OSAS ($n = 78$)	Controls ($n = 89$)	
RLSh absent		57 (73%)	76 (85%)	*					
RLSh present		21 (27%)	13 (15%)	*	4 (5%)	1 (1%)	17 (22%)	12 (13%)	ns
	<10 MB						13 (17%)	11 (12%)	ns
	$\geq 10 < 20$ MB						1 (1%)	1 (1%)	ns
	≥ 20 MB −c				4 (5%)	1 (1%)	3 (4%)	0 (0%)	ns
	≥ 20 MB +c						0 (0%)	0 (0%)	ns

RLSh, right-to-left shunt; MB, microembolic signals; −c, without curtain; +c, with curtain; ns, not significant; *, $P < 0.05$.

prevalence of large RLSh between OSAS and controls (Table 1). The logistic regression applied to the occurrence of RLsh in the OSAS sample by means of the stepwise procedure did not reveal any relevant regressors among the parameters studied.

4. Discussion

Our data confirm the results of a recent study [25]. From a statistical point of view, prevalence of PFO in OSAS is significantly higher when compared with the control group. Furthermore, shunt is frequently present only during Valsalva maneuver. Nevertheless, our study did not confirm the high prevalence reported in this prior report (69% in OSAS ($n = 48$) vs. 17% in control group ($n = 24$)). Differences seem to be smaller. In fact, the prevalence of RLSh in both our OSAS sample and our control group fall in the normal range.

The observed trend towards a higher prevalence of PFO in subjects with OSAS compared with the control group could be explained by the enhanced effort on the right side of the heart due to transient but frequent elevations of right-sided pressure during apnea [33,34]. A similar increased prevalence of PFO due to chronic right-sided pressure elevation has also been observed in subjects with severe chronic obstructive pulmonary disease [20,21]. Both these mechanisms, from a theoretical point of view, could cause the reopening of a previously closed foramen ovale. However, the data from our study cannot confirm this hypothesis because increased prevalence of PFO within the large magnitude (>20 microembolic signal) in the OSAS sample with respect to normal controls could not be found.

A previous study by our group [22] showed that RLSh through a PFO is achieved not only during the execution of the Valsalva maneuver but also during spontaneously occurring obstructive sleep apneas. Obstructive apnea starts with an inspiratory effort against a closed upper airway (i.e. Müller maneuver), followed by sequences of other Müller maneuvers; if obstructive apnea is long enough, the likelihood of alternating sequences between Müller and Valsalva maneuver increases [33]. However, Valsalva maneuvers, which occur in the latter part of obstructive apnea, seem to give rise to only a relatively small increase in end-expiratory pleural pressures in contrast to the relatively large decrease in end-inspiratory pleural pressures (i.e. Müller maneuver) [33,34]. Therefore, the occurrence of RLSh during apnea probably does not correlate simply with the magnitude of Müller or Valsalva maneuver per se, but rather with their swings of increasing and decreasing effects on the pleural pressure. This could directly influence the interatrial pressure balance and the increase of inspiratory venous return, with a consequent right-sided pressure increase, enhancing the likelihood of RLSh through a PFO.

Recently. it has been shown that the diameter of PFO is an independent risk factor for ischemic events, especially recurrent strokes [35,36]. In subjects with OSAS a higher risk for cerebrovascular disease compared to the normal population is well documented [37,38]. Previous studies, however, correlated the high prevalence of stroke in OSAS only with factors unrelated to the presence of PFO, especially hematological features. The common final pathway of these features consists in the increase of whole blood viscosity [39]. These hematological alterations give rise to the reactive polycythemia in subjects with OSAS, increasing the likelihood of microemboli. Therefore, the presence of a PFO could increase the likelihood of microembolic passages during nocturnal sleep with obstructive apneas or other conditions similar to the Valsalva maneuver. There is a high likelihood of these respiratory events occurring during sleep in OSAS subjects. In fact, clinical practice shows that among these subjects respiratory events can range from ten to more than 100 apneas per hour. Therefore, in our view, tempestive diagnostic investigations into the presence of PFO in OSAS subjects could be an important feature in an attempt to decrease the risk for stroke, permitting approaches of surgical closure of PFO and/or life-long treatment with anticoagulants or antiplatelet agents [40]. Finally, further investigations are needed to evaluate the role of ventilatory treatment with continuous positive air pressure to reduce the risk for stroke in these patients by preventing apnea, and thus the likelihood of RLSh.

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