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The influence of patent foramen ovale on oxygen desaturation in obstructive sleep apnoea

Running title: PFO in OSA

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Abstract

Aims

Obstructive sleep apnoea (OSA) is associated with oxygen desaturation to a varying degree. Patent foramen ovale (PFO) may allow interatrial right-to-left shunting. The hypothesis of the study is that oxygen desaturation will occur more often, proportionally to the frequency of respiratory disturbances, in OSA subjects with PFO than in those without.

Methods

In a group of 209 subjects diagnosed with OSA, the proportion of desaturation to respiratory events was calculated as the ratio of "oxygen desaturation index /apnoea-hypopnoea index" (ODI/AHI). Fifteen cases with high proportional desaturation (ODI/AHI≥0.66) were individually matched with 15 controls with low proportional desaturation (ODI/AHI≤0.33), all without pulmonary disease. PFO was assessed with contrast transoesophageal echo and considered large when at least 20 bubbles passed over to the left atrium after a single injection.

Results

The prevalence of large PFO was 9 out of 15 (60%) in the high-proportional desaturation group, versus 2 out of 15 (13%) in the low-proportional desaturation group (p=0.02). The median number of passing bubbles was positively correlated to minimum oxygen saturation among those with PFO (r=0.62, p= 0.02).

Conclusion

Oxygen desaturation occurs more often proportionally to the frequency of respiratory disturbances in OSA subjects with PFO than in those without.

Key Words

Echocardiography, heart septal defects, hypoxia, obstructive sleep apnoea, patent foramen ovale.

Introduction

Obstructive sleep apnoea (OSA) is a common disorder that affects 5-15 % of the middle-aged population and has been identified as a risk factor for cardiovascular disease (1-3). Patent foramen ovale (PFO) is also a common condition, present in 25% of the adult population and constituting a risk factor for cryptogenic stroke as well as a potential contributor to hypoxaemia in patients, both with and without pulmonary disease (4-7). PFO and OSA are often considered to be two separate entities that are not interrelated; however, as both have a high prevalence they sometimes co-exist and may influence the patophysiology of each other. Obstructive apnoea provokes excessive intrathoracic pressure swings that greatly influence the central haemodynamics, thereby creating a right to left shunt through the PFO, which may cause significant desaturation (8-13). This may explain why more severe desaturation than predicted from alveolar hypoventilation has been demonstrated in OSA patients (14-16). This study hypothesises that desaturation will occur more often proportionally to the frequency of respiratory disturbances in OSA subjects with PFO than in those without.

Methods

Selection of study population

The study population was selected from a community-based sample described in the Skaraborg sleep study (17). In short, 161 patients with hypertension and 183 subjects without hypertension were subjected to polysomnography, without consideration of any clinical symptoms of sleep apnoea. In total, 209 subjects were diagnosed with OSA. The oxygen desaturation index/apnoea-hypopnoea index (ODI/AHI) ratio was calculated for each of the 209 subjects. They were then ranked in accordance with their ODI/AHI ratios and divided into tertiles. The subjects with the lowest and highest ratio (≤0.33 and ≥0.66, tertile extremes) were considered for inclusion. Those with a ratio ≤0.33 were defined as low proportional desaturation (low PD, 54 subjects) and those with a ratio ≥0.66 as high proportional desaturation (high PD, 57 subjects). Study participants were divided into pairs by contrasting their ratio and 15 pairs with the highest and the lowest ratio were chosen with the aim of maximising the difference in desaturation between the subjects within each pair in order to test the study hypothesis. The subjects were matched for the presence of hypertension (with or without diabetes) body mass index (within 3 kg/m²) and age (within 5 years). When more than one match was available the minimum oxygen saturation and the mean overnight oxygen saturation were also considered in a manner that generated maximum difference. When a pair was split by one of the participants being excluded or not giving consent a second best match for the first subject was chosen. Following this procedure, 64 subjects were evaluated for participation before the final 15 matched pairs were finally identified. Exclusions were based on: death (n=2), obstructive pulmonary disease (n=7), other diseases (n=3), or by subjects not giving consent (n=22). Characteristics of the subjects are described in Table 1. All participants gave written informed consent to participate. The study was approved by the Gothenburg University human research ethics committee.

Polysomnography

The in-home, full-night polysomnography recording used a computerised recording system (Embla A10©, Flaga, Reykjavik, Iceland) consisting of: 1) sleep monitoring through three-channel electroencephalography, two-channel electrooculography, and one-channel submental electromyography; 2) bilateral tibial electromyography and a body-position detector; 3) two-lead

electrocardiogram; and 4) respiration monitoring through an oro-nasal thermistor as well as nasal pressure sensor for apnoea-hypopnoea detection. Piezo crystal effort belts were used for thoracic-abdominal movement detection and a pulse oximeter (Embla Oximeter-XN) was applied. The sensors were applied and the equipment calibrated at the primary care centre by a certified sleep technician or specially trained local staff. Data was subsequently scored, based on 30-second epochs according to the Rechtschaffen and Kales criteria (18). An overall sleep stage report and accurate measures of respiratory events during the sleeping period were generated. Respiratory events were scored in accordance with guidelines for measurements in clinical research (19). Obstructive apnoea (hypopnoea) was defined as a flat (≥40 % reduction of) nasal pressure signal accompanied by respiratory effort movements for ≥10 sec and desaturation ≥3 % from the immediately preceding baseline, or arousal. The definition of both apnoea and hypopnoea included the same requirement of ≥3 % desaturation and/or arousal. The apnoea-hypopnoea index (AHI) was calculated to define the number of episodes of apnoea and hypopnoea per hour of sleep. OSA was defined as AHI ≥10 obtained through sleep recording with a total sleep time of at least 4 hours. The oxygen desaturation index (ODI) was defined as the number of episodes per hour of sleep with a reduction in saturation of at least 4 % from baseline, and ≥10 seconds.

Daytime sleepiness was assessed with the Epworth Sleepiness scale, an eight-item self-administered questionnaire used for rating the likelihood of dozing in eight daily situations on a scale of 0-3. The final score ranges from zero (no daytime sleepiness) to 24 (maximum daytime sleepiness) (20).

Spirometry

Standard dynamic spirometry (Spirotrac, Vitalograph, Ennis, Ireland) was performed on the same day as the TE examination in all subjects. Values were calculated as percentages of predicted values (21, 22). Daytime percutaneous oxygen saturation was measured with the Ohmeda Biox 3740 (Ohmeda, Lousville, CO, USA).

Transesophageal contrast echocardiography

One person (MJ) from March to December 2003 performed all examinations. Subjects were instructed and trained to perform the Valsalva manoeuvre with at least 40 mmHg during 8 seconds. The achieved pressure was shown to the subject using a manometer. Multiplane transoesophageal echocardiography was performed (Siemens, Acuson Sequoia256 or General Electric, Vivid 7) after mild sedation with midazolam and local pharyngeal anaesthesia (lidocain). Colour Doppler with reduced pulse repetition frequency to about 40 cm/second and repeated contrast injections were used to detect PFO. A gelatin-based plasma expander (3.5% polygelin, Aventis Pharma, Frankfurt am Main, Germany) and a small amount of air (5-10% mixture) was agitated between two syringes mounted on a three-way stop-cock immediately before a bolus injection via a 20-gauge venous canula (23). Two-ml injections were administered antecubitally while 10ml injections were administered via the foot vein, followed by a bolus injection of 5-10 ml of saline. Contrast injections were given according to a standardised protocol that included injections during relaxed breathing in the supine and left lateral cubitus position and multiple provocations such as Valsalva manoeuvre, coughing and bed tilt (24, 25). In order to reduce preload, nitroglycerin (0.8 mg) was sprayed lingually, during 10-degree foot-down bed tilt, and contrast was injected antecubitally during relaxed breathing and Valsalva. Antecubital injections were made a few seconds after start of the Valsalva manoeuvre with the aim to maintain strain for about 10 seconds and make the septum primum bulge over towards the left atrium, at the very same moment as the region in the right atrium adjacent to the fossa ovalis was filling with contrast (26). When this failed, the timing of Valsalva versus contrast injection was adjusted and the procedure repeated. Foot vein injections were made a few seconds before the start of the Valsalva manoeuvre.

PFO analysis

The echo evaluation was performed off-line from Super-VHS video and blinded to the polysomnography results and patient group allocation. A PFO was defined as a minimum of three bubbles in the left atrium adjacent to the septum within three heartbeats from contrast filling of the right atrium.(25). The number of bubbles passing into the left atrium was estimated. A large PFO was defined as a minimum of 20 accumulated bubbles passing over after a single injection (5). PFO analysis was made

independently by two persons (MJ+PE), during 2003 and 2004. Disparities were settled by consensus with a third observer.

Transthoracic echocardiography

Standard echo-doppler examinations were performed in all subjects. Left ventricular mass was calculated according to the corrected formula of the American society of echocardiography and indexed for body surface area. The longitudinal, myocardial, peak systolic and early diastolic velocities was assessed in the base of the left ventricular lateral wall and in the base of the right ventricular wall with spectral, pulsed-wave tissue Doppler. The left ventricular ejection fraction was visually estimated. The systolic maximum tricuspid regurgitation gradient was assessed with and/or without signal amplification with agitated polygelin as echo contrast. Right atrial pressure was quantified on the basis of the respiratory variations of the inferior vena cava width and the right ventricular systolic pressure was calculated as the sum of the right atrial pressure and tricuspid regurgitation gradient. The left and right atrial area was measured in apical four-chamber view in end systole.

Statistical analysis

Hypothesising a minimum of 60 % PFO prevalence in high PD subjects and a maximum of 15 % in low PD subjects, we calculated that a sample of 15 pairs would give 80 % power to detect the difference with a level of significance of $p<0.05$. McNemar's two-tailed test was used for paired proportions. For comparison of the prevalence between groups Fischer's two-tailed exact test was used, for quantitative parameters the Student t-test was used and for correlation Pearsson's test was used. A p value < 0.05 was considered statistically significant. All values are given as means ± 1 standard deviation, unless otherwise stated.

Role of funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

All 30 subjects completed contrast TE with 12 to 20 injections each. A PFO was found in 14 (47%) subjects and was classified as small in 3 and large in 11 subjects. The PFO subjects received 17. 6±1.6 and the non-PFO subjects received 18.4±2.2 injections. A large PFO was found in 9 of the 15 (60%) high PD cases but only in 2 of the 15 (13%) low PD controls (p=0.02), as shown in Figure 1. Furthermore, the PFOs were found in individuals with a large range of AHI values as shown in Figure 2. The paired distribution showed a higher prevalence of large PFOs in high PD cases than in low PD controls. There were 8 pairs in which only the high PD case had a large PFO, one pair in which both had a PFO, 5 pairs in which no large PFO was found, while in 1 pair only the low PD control had a large PFO ($p<0.04$). The paired distribution regarding all-size PFO did not reach a statistically significant difference (p=0.07). **The predictive value of the ODI/AHI ratio for PFO detection was calculated. A high ratio (≥0.66) had a sensitivity of 82% and a positive predictive value of 60%. A low ratio (≤0.33) had a specificity of 68% and a negative predictive value of 87%.** The spirometry and polysomnography data for the groups are shown in Table 2. As expected, the ODI is higher in high PD cases than in low PD controls. But the significant difference is not explained by AHI. In fact, the AHI was not significantly different between groups. No significant difference in AHI, apnoea index or apnoea duration was found regarding the presence or absence of a large PFO. However, the ODI/AHI ratio in large PFO subjects was twice that found in subjects without a large PFO. The ODI/AHI ratio, but not the minimum oxygen saturation and ODI *per se*, was fairly well correlated to a large PFO (r=0.55, p=0.02). The median number of bubbles passing into the left atrium after an injection was significantly correlated among all 30 subjects with nocturnal minimum oxygen saturation (r=0.36, p=0.05) and among the 14 subjects with a PFO (r=0.62, p= 0.02). However, age, body mass index, hypertension, diabetes and blood pressure did not differ in accordance with the PFO diagnosis. The measured echo parameters did not differ between groups, as shown in Table 3.

Discussion

To the best of our knowledge, this is the first study demonstrating an association between nocturnal desaturations in OSA and the existence of PFO. In order to discriminate between desaturation caused by veno-arterial admixture and desaturation caused by apnoea-hypopnoea-related interruption in alveolar ventilation, we calculated the ODI/AHI ratio for each OSA subject. This ratio is a novel construction that consists of two well-defined parameters with the same denomination; number per hour of sleep. The ODI and AHI values were fairly well correlated to each other among those 209 OSA subjects from whom the 30 study subjects were selected ($r=0.8$ $p<0.01$). Also in the literature, ODI is generally considered to be positively correlated to AHI in OSA subjects (27). Because of this correlation, we consider the ODI/AHI ratio to be a factor that roughly corrects the desaturation frequency for the apnoea-hypopnoea frequency and that its variation reveals that other factors than ventilation could be involved. Although the correlation is good in a group of OSA subjects, large variations are actually found when AHI and ODI are compared between individual subjects (27). In the whole group of 209 subjects with OSA, the AHI values were generally higher than the ODI values with a mean difference of 15.8 and a considerable scatter (SD 13.7). According to our hypothesis a subject with ODI 16 and AHI 20 (ODI/AHI=0.8) would be more likely to have a PFO than a subject with ODI 10 and AHI 40 (ODI/AHI=0.25), even though the OSA is more severe in this latter subject. As shown in Table 2, pulmonary function was significantly better in high PD cases than in low PD controls, supporting the hypothesis that other factors than respiratory factors are involved. Moreover, the variation in ODI/AHI ratio between groups was not explained by the AHI. However, the power of the ODI/AHI ratio to predict shunt-related desaturation is limited. The magnitude of desaturation from an interatrial shunt will depend on the size of the PFO, and the interatrial pressure relation. The potential opening diameter of the PFO varies between at least one and 19 mm (4). Since the number of bubbles passing through is only a rough estimate of the diameter during balloon sizing, and no catheterisation was performed, we do not know the exact maximum opening diameter (28). The interatrial pressure relationship will depend on the degree of right-heart loading during obstructive apnoea but also on concomitant left-heart condition.(23) Shunt diagnosis was only performed with the

subjects awake, for which reason the actual degree of shunting during sleep is unknown. In order to overcome this weakness we focused on the frequency of moderate desaturation (>4%) rather than maximum desaturation. The study of Beelke et. al. found right-to-left shunting in 9 out of 10 PFO subjects during obstructive apnoea lasting longer than 17 seconds but not during hypopnoea (29). That study exclusively included OSA subjects with apnoea-hypopnoea and concomitant 4% desaturation, which would correspond to the high PD cases in the present study. One of the two low PD controls with PFO in our study had only hypopnoeic and no apnoeic events while the other had only three episodes of apnoea per hour of sleep. Our results is in contrast, in part, to the study of Shanoudy et.al., which showed a generally increased prevalence of PFO in OSA, but did not consider the degree of desaturation in relation to apnoeic events (12). Our study showed a low prevalence of only 13 % in the low PD group. It also seems logical that PFO is not a cause of upper airway obstruction, but its valve-like function permits unidirectional right-to-left shunting during right-heart loading, such as that occurring during obstructive apnoea (8, 9, 29). The analysis of PFO is not always distinct. There was disagreement in the analysis of one large PFO and of three small PFOs; however, they were all solved through consensus. This is in concordance with Cabanes et. al., who found considerable variation in small-PFO analysis with only a few bubbles passing to the left atrium (25), However the clinical significance of these small shunts is probably very limited (5). In our study, the PFO channel was visualised in nine subjects, all with large PFO, whereas in the other subjects, the exact location of the passage could not be visualised. Another route of contrast passage could hypothetically be intrapulmonary shunts, but this is probably not the case as contrast appeared in the left atrium adjacent to the septum within three heartbeats from contrast filling of the right atrium. The current sampling and classification procedure may have been skewed towards high AHI values in this population, as the definition of respiratory events was based on nasal pressure canula recording. Moreover, obstructive events were also scored when respiratory events included arousal but not necessarily desaturation. This practice may also have elevated the AHI value in patients with minor desaturation but frequent arousal responses. Apnoea duration and the relationship between episodes of apnoea and hypopnoea may also have introduced a confounding influence. In calculating ODI/AHI we counted apnoeas and hypopnoeas together, although shunting seems to occur only during apnoeas (29). The

high PD cases without PFO had significantly more hypopnoeas than those with PFO (Table 4). Frequent hypopnoeas in OSA subjects have been associated with reduced hypoxic ventilatory drive (30). This may cause high a ODI/AHI ratio because of reduced ventilation between events and relatively low respiratory event scoring, as the baseline respiratory flow also is reduced.

This study supports the hypothesis that interatrial shunting gives a substantial increase in the number of desaturations in OSA subjects with PFO. Moreover, this may be the mechanism that explains the increased risk of stroke that is seen in OSA (31). If this could be established, percutaneous closure of a PFO may be a potential treatment option in the future (32). A strength of the study is that it was based on a cross-sectional population sample randomly selected for polysomnography without prior knowledge of sleep disturbances. Subjects diagnosed with OSA were considered for inclusion on the basis of their ODI/AHI ratio and with obstructive pulmonary disease as the only exclusion criterion. Although the study group was small, the findings may therefore be regarded as reasonably applicable to a general, pulmonarily healthy, population of subjects with OSA.

Conclusion

Oxygen desaturation occurs more often in proportion to the frequency of respiratory disturbances in OSA subjects with PFO than in those without. The ODI/AHI ratio might be a clinically useful screening tool, able to select OSA subjects with a high likelihood of PFO.

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Figure legends

Figure 1

Title: Distribution of PFO subjects according to ODI/AHI ratio.

Legend: White bar=subject with large PFO; Hatched bar=subject with small PFO; Black bar=subject without PFO; ODI/AHI= "Oxygen Desaturation Index/Apnoea Hypopnoea Index"; PFO=Patent Foramen Ovale; low PD = low Proportional Desaturation (ODI/AHI≤0.33); high PD= high Proportional Desauration (ODI/AHI≥0.66). One subject without PFO had ODI/AHI=0

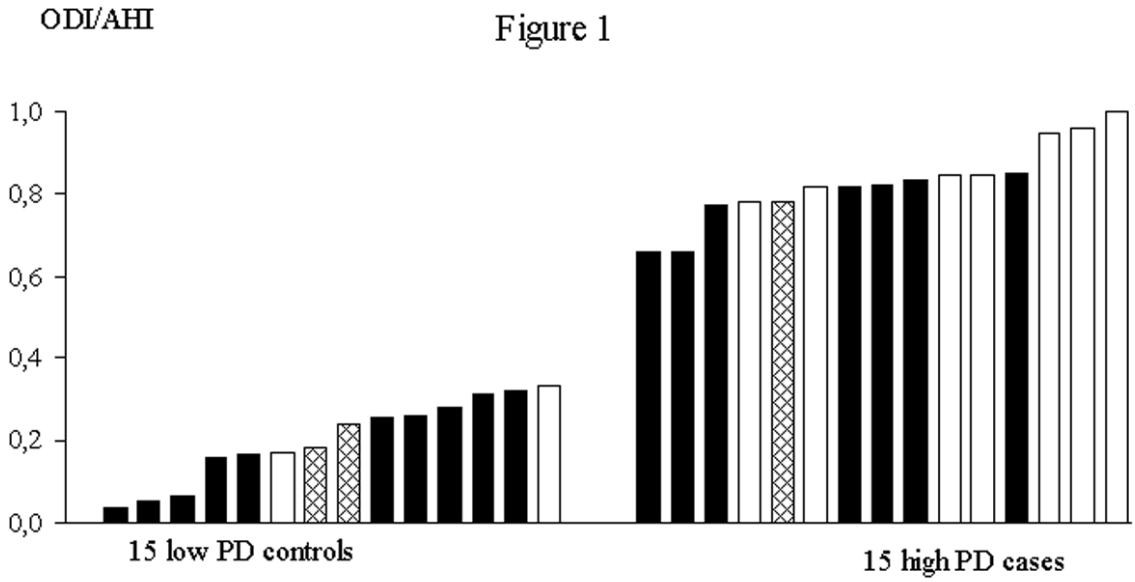

Figure 2

Title: Correlation of ODI/AHI and AHI among subjects with and without PFO.

AHI=Apnoea Hypopnoea index; ODI=Oxygen desaturation index. According to our thesis it is more likely that a subject in the upper part of the graph would have a PFO than a subject in the lower part, irrespective of AHI value. PFO: = Patent Foramen Ovale

Figure 2

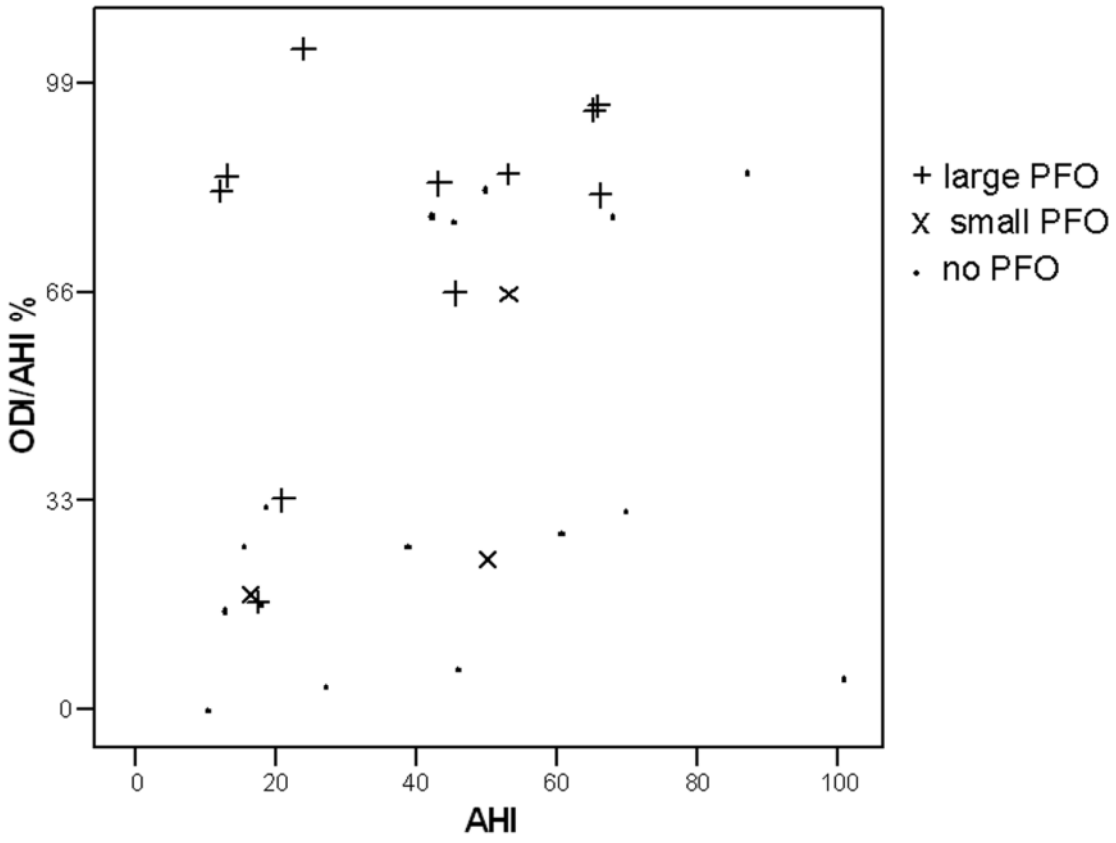
99
66
33
0
ODI/AHI %
0
20
40
60
80
100
AHI
+ large PFO
x small PFO
· no PFO

Table 1. Descriptive characteristics of matched groups

	High PD n=15	Low PD n=15	P
Age (y)	60.3 ±5.2	61.0±5.8	n.s.
Male n. (%)	12 (80.0)	8 (53.3)	0.13
BMI (kg/m²)	29.6±3.8	29.8±3.7	n.s.
Hypertension n. (%)	8 (53.3)	8 (53.3)	n.s.
SBP (mmHg)	141±16	141±18	n.s.
DBP (mmHg)	81±10	80±8	n.s.
Diabetes n. (%)	2 (13.3)	2 (13.3)	n.s.
Smoking n. (%)	1 (6.7)	2 (13.3)	n.s.
ESS	6.3±3.5	6.7±3.4	n.s.

High PD=High Proportional Desaturation=Oxygen Desaturation Index/Apnoea-Hypopnoea Index=(ODI/AHI) ≥0.66; Low PD=Low proportional desaturation=ODI/AHI≤0.33; BMI=Body Mass Index,; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; ESS= Epworth Sleepiness Scale; n.s.=non-significant; P value unless p>0.2.

Table 2. Spirometry and polysomnography data in the matched groups and in subjects with vs. without large PFO

	Proportional Desaturation			Large PFO		
	High PD n=15	Low PD n=15	P	Yes n=11	No n=19	P
VC (%)	87.9±12.1	85.5±17.4	n.s.	90.0±13.5	84.8±15.5	n.s.
FEV1 (%)	97.1±15.9	86.7±17.7	0.10	97.3±19.0	88.8±16.0	0.20
PEF (%)	92 .2±18.5	77.2±12.4	0.02	93.0 ±20.0	79.9±13.8	0.07
OS (%) daytime	95.4±2.1	96.0±2.0	n.s.	95.4±2.3	95.9±1.9	n.s.
OS mean (%) sleep	93.0±1.7	95.2±1.7	0.02	93.3±1.8	94.5±2.0	0.09
OS min (%) sleep	75.4±7.5	84.7±2.9	<0.001	78.3±6.7	81.1±7.6	0.18
Desat 10 (%)	10.1±11.0	0.0±0.0	0.003	9.0±12.9	2.8±5.4	0.15
ODI (n/hour)	40.5±18.4	6.5±6.2	<0.001	31.5±22.3	18.9±20.9	0.14
AHI (n/hour)	48.9 ±20.8	34.9±26.1	0.12	38.8±22.0	43.7±25.90	n.s.
ODI/AHI	0.83±0.10	0.19±0.11	<0.001	0.75±0.27	0.37±0.30	0.001
AI (n/hour)	26.7±20.7	9.9±16.6	0.021	23.6±21.9	15.2±19.2	n.s.
Apnoea duration (sec)	25.0±9.1	16.8±8.0	0.014	23.3±12.6	19.5±6.9	n.s.
HI (n/hour)	21.9±13.1	25.0±14.9	n.s.	14.7±7.2	28.5±14.4	0.007
Hypopnoea duration (sec)	28.3±8.4	23.6±3.6	0.06	26.9±7.9	25.4±6.2	n.s.

P value unless p>0.2; High PD=High Proportional Desaturation (ODI/AHI≥0.66); Low PD=Low Proportional Desaturation (ODI/AHI≤0.33); PFO=Patent Foramen Ovale; VC=Vital Capacity; FEV1= Forced Expiratory Volume in 1 second; FEV%=FEV1/VC; PEF=Peak Expiratory Flow. All values for spirometry data given as percentage of predicted value. OS= oxygen saturation percutaneously measured; ODI/AHI="Oxygen Desaturation Index/Apnoea Hypopnoea index"; AI=Apnoea Index (number of episodes of apnoea per hour of sleep); HI=Hypopnoea Index (number of episodes of hypopnoea per hour of sleep); Desat 10=episodes per hour of sleep with desaturation of more than 10%.

Table 3. Echocardiography data in the matched groups and in subjects with vs. without large PFO

	Proportional Desaturation			Large PFO		
	High PD n=15	Low PD n=15	P	Yes n=11	No n=19	P
LVMI (g/m²)	123±26	122±28	n.s.	117±26	126±28	n.s.
EF (%)	58±3	58±4	n.s.	59±3	59±4	n.s.
Sm cm/s	13.2±4.0	12.9±2.6	n.s.	12.8±2.9	13.5±4.1	n.s.
Em (cm/s)	12.6±2.9	12.3±2.2	n.s.	12.3±2.9	12.6±2.4	n.s.
E/Em	5.7±1.3	6.0±1.4	n.s.	5.9±1.2	5.8±1.4	n.s.
Sm_{RV}	18.6±6.0	18.0±5.1	n.s.	19.3±5.3	17.8±4.8	n.s.
Em_{RV}	16.9±6.8	16.7±3.8	n.s.	16.6±8.0	17.0±3.5	n.s.
E_{RV}/Em_{RV}	3.3±1.1	3.1±0.7	n.s.	3.2±1.1	3.2±0.8	n.s.
RAP (mmHg)	6.0±2.1	5.0±0	0.08	5.5±1.5	5.5±1.6	n.s.
RVSP (mmHg)	27.8+6.5	26.8±3.3	n.s.	27.3±7.2	27.3±3.6	n.s.
LA area	20.4±4.6	21.5±4.3	n.s.	19.4±4.0	21.8±4.5	n.s.
RA area	16.9±3.6	16.2±2.7	n.s.	16.5±3.1	16.5±3.2	n.s.

P-value unless p>0.2; High PD=High Proportional Desaturation (ODI/AHI≥0.66); Low PD=Low Proportional Desaturation (ODI/AHI≤0.33); PFO=Patent Foramen Ovale; LVMI=Left Ventricular Mass Index (gram/m² body surface area); EF= Left ventricular Ejection fraction; Sm=peak systolic velocity of LV myocardium; Em= Early diastolic left ventricular Myocardial relaxation velocity; E/Em= ratio between Early diastolic transmitral inflow velocity and Em; Sm_{RV} = peak Systolic

velocity of the Right Ventricular Myocardium; Em_{RV}=Early diastolic Right Ventricular Myocardial relaxation velocity; E_{RV}/Em_{RV}=ratio between Early diastolic transtricuspid inflow velocity and Early Myocardial Right Ventricular relaxation velocity; RAP=Right Atrial Pressure; RVSP=Right Ventricular Systolic Pressure; LA area=Left Atrial area; RA area= Right Atrial area.

Table 4. Characteristics of high PD cases according to presence of large PFO.

Large PFO	Yes=9	No=6	P
ODI/AHI	0.86±0.11	0.78±0.07	0.08
AHI (n)	43±22	58±17.0	0.18
HI (n)	14.0±7.7	34±10.3	0.003
AI (n)	28.6±21.4	23.8±21.3	n.s.
Hypopnoea, min per hour	5.8±2.4	14.8±5.1	0.006
Apnoea, min per hour	14.0±12.9	9.2±8.9	n.s.

Abbreviations as in Table 2.