

Research Article

Respiratory and Endothelial Dysfunctions in Case of Obstructive Sleep Apnea-Hypopnea Syndrome

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Abstract

Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) is commonly associated to cardiovascular involvements by an endothelial dysfunction mechanism.

Objective: Confirm respiratory dysfunction and analyze the central and peripheral vascular dysfunction in cases of OSAHS.

Methods: It is a cross-sectional study on 49 adult subjects: 23 suffering from OSAHS and 26 obese controls. All subjects underwent polysomnography or sleep polygraphy, lung function tests (total body plethysmography, measure of transfer factor of the lung for carbon monoxide (DLCO) and Fraction of Exhaled Nitric Oxide (FeNO)), Laboratory tests, and measurement of endothelial function by evaluating endothelium dependent vasodilatation (VDED) upon the combination of acetylcholine iontophoresis and blood flowmeter by Laser Doppler.

Results: A significant decrease in lung function is noted in patients with OSAHS compared to controls. Indeed the OSAHS group has a tendency to pulmonary restriction with an abnormal DLCO and to bronchial inflammation (increased FENO) when compared to control group. A greater impairment of VDED in all patients with OSAHS than in healthy is also confirmed.

Conclusion: The abnormality of alveolar-capillary diffusion in apneic patients can be explained in part by bronchial inflammation and endothelial dysfunction.

Keywords: DLCO; Endothelial function; Lung function; Exhaled nitric oxide; OSAHS

Introduction

Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS), defined as Apnea-Hypopnea Index (AHI) > 10/h [1-4], currently represents a real public health problem, with an adult prevalence of 2% to 4% [5]. The origin of sleep apnea may be central (stopping central control of breathing) or constitutional device, due to an abnormality of the upper airways or dilator muscles of the pharynx. Obstructive apnea corresponds to a stop of the naso-oral ventilation with persistence of thoraco-abdominal movements [6]. Severe snoring and daytime somnolence clinically evoke the diagnosis of OSAHS, but there are no specific symptoms [7]. Polysomnography in the sleep laboratory remains the main tool for diagnosis of OSAHS [8,9].

Although the prevalence of different ventilatory defects in OSAHS is poorly known and the studies analyzing their plethysmographic profile are contradictory [10], ventilatory variables remain considered as predictive factors of mortality and morbidity for patients having OSAHS [11,12]. It is true that the realization of a plethysmography is not systematic in OSAHS since it is recommended only in certain situations: obesity, smoking and presence of respiratory symptoms

[8,9,13]. However international respiratory societies recommend their use for the diagnosis of any ventilatory dysfunction. This is why we think it is interesting to establish the plethysmographic profile of patients with OSAHS as well as that of the controls according to the recent international recommendations [10,11,14].

The OSAHS can have many serious consequences: metabolic, behavioral or cardiovascular (coronary insufficiency, hypertension) [6,7,13,15-17]. These latter consequences are common in patients with OSAHS, but the underlying mechanisms of this association are largely unknown. Several hypotheses evoke an alteration of endothelial tissue as a mechanism of these vascular complications in case of SAHOS [18]. Thus, the evaluation of the endothelium-dependent response of the peripheral vessels seemed important to us to study the SAHOS-vascular endothelial relationship. Thus, the objectives of this work are

- To compare the respiratory function of patients with OSAHS compared with obese non-apneic patients.
- Evaluate pulmonary and peripheral vascular dysfunction case of OSAHS by measuring carbon monoxide transfer capacity (DLCO) and peripheral vascular reactivity respectively.

Materials and Methods

Study design

This is a cross-sectional study conducted in the physiology and functional exploration laboratory. The studied sample is composed of two groups of adults aged 20 years to 65 years. A control group G1 that is composed of 25 subjects obese and free from any respiratory disease. A group of apneic subjects (G2, N=23) who consulted for excessive daytime sleepiness and snoring at the Sleep Pathology Unit and an OSAHS was diagnosed by polysomnography. Subjects from G2 have the following characteristics: an age between 20 years and 65

Citation: Rouatbi S, Ghannouchi I, Kammoun R, Bechikh R, Saad HB. Respiratory and Endothelial Dysfunctions in Case of Obstructive Sleep Apnea-Hypopnea Syndrome. *Gen Surg.* 2019; 1(3): 1014.

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Publisher Name: Medtext Publications LLC

Manuscript compiled: Dec 06th, 2019

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years old, obesity and a confirmed OSAHS with an AHI greater than or equal to 10.

Subjects with one or more of the following criteria were excluded from the study [18]: An intercurrent respiratory infection of the upper or lower respiratory tract, an asthmatic disease or Chronic Obstructive Pulmonary Disease (COPD), a known neuromuscular pathology, an upper airway abnormality, imperfect performance of required breathing maneuvers, and smoking >10 pack year [19].

Survey

All subjects responded to a standardized questionnaire seeking inclusion and non-inclusion criteria, respiratory function signs (cough, dyspnea, expectoration, snoring, daytime sleepiness) and anthropometric characteristics: Sex, Age (years), Weight (Kg), Height (m) and Body Mass Index (BMI, kg/m²) calculated according to the BMI formula = Weight/Height². Based on BMI value, 3 classes of obesity have been defined according to WHO are Obesity class 1: BMI between 30 kg/m² and 34.9 kg/m², Obesity class 2: BMI between 35 kg/m² and 39.9 kg/m² and Obesity class 3: BMI greater than 40 kg/m² [20,21].

Functional respiratory explorations: Total body plethysmography

All patients and subjects of the study performed a total body plethysmography using "ZAN 500" equipment (Messgeraete GmbH2000, Germany).

As recommended by recent international guidelines, ventilatory variables are interpreted according to local reference values [11]. The total body plethysmography allows the measurement of ventilatory flows (forced expiratory volume at the first second (FEV₁, l/s and %), median maximum expiratory flow (MEF₂₅₋₇₅, l/s and %), maximum expiratory flow at x% of FVC (MEF₂₅ and MEF₅₀, l/s and %)). The measured pulmonary volumes are: slow vital capacity (VC; l and %), forced vital capacity (FVC; l and %), FEV₁/VC ratio (%), total lung capacity (TLC, l and %) and residual volume (RV, l and %).

Measured parameters by plethysmography are considered diminished when they are below the Lower Limit of Normal (LLN). The LLN is determined from the specific reference values of the Tunisian population [22].

In this study, we defined different ventilatory defects: proximal obstructive ventilatory defect is when the ratio FEV₁/VC or FEV₁/FVC is lower than the LLN [11]. Distal obstructive ventilatory deficit is defined when the FEV₁/FVC ratio is normal, the FVC is normal and MEF₂₅ or MEF₅₀ or MEF₂₅₋₇₅ is less than the LLN. A restrictive ventilatory defect is defined by the TLC which is lower than LLN. Static pulmonary distension is defined as an increase in RV that is greater than the Upper Limit of Normal (ULN) [11].

Measure of carbon monoxide transfer capacity (DLCO)

DLCO (mmol/KPa/min) is measured by the inspiratory apnea method. This parameter is considered diminished when it is lower than the LLN [11].

Polysomnography

Overnight PSG is performed using DeltaMed (France, Coherence 4 NT) and Nihon Kohden (Japan, 2011) for PSG performed after 2012. Sleep states were assessed by recording biopotentials (electroencephalogram, electromyogram, electrooculogram), qualitative recordings of respiratory effort (piezo sensors), airflow

(thermal sensors), and oxygen saturation (pulse oxymetry). The sampling frequency for the equipment DeltaMed is 256Hz and 500Hz for Nihon Kohden. Respiratory events are apneas and hypopneas. Obstructive apnea is defined as naso-oral airflow arrest for at least 10 seconds with persistent ventilatory efforts during apnea [1,3,6].

Hypopneas are defined as a reduction of more than 50% of the oronasal flow amplitude during 10 sec, accompanied by 3% desaturation and/or arousal. The AHI is the number of apneas and hypopneas per hour of sleep [23,24]. The severity of OSAHS is defined according to the value of AHI: light OSAHS AHI<15, moderate OSAHS: 15<AHI<30, severe OSAHS: AHI>30 [25]. Polysomnographic scoring and staging are based on Rechtschaffen and Kales study, and episodes of arousals are assessed according to the guidelines in the previous studies [26].

Measurement of exhaled nitric oxide

Exhaled Fraction of Nitric Oxide (FeNO) is measured by the Medisoft HypAir method using an electrochemical analyzer (Medisoft, Sorinnes, Belgium). It is based on the chemiluminescence method [27]. The instrument has been calibrated and used according to the manufacturer's instructions. The measurement of FeNO is made following the international recommendations. Three acceptable measurements are taken at a flow rate of 50 ml/s at 15 minutes as recommended by the ATS/ERS. The average of the three values used. FeNO is expressed in parts per billion (ppb), which is the equivalent of nanoliter per liter [27].

Endothelial function study: Laser Doppler

A technique studies the microcirculation and can therefore visualize the subcutaneous blood flow variation (qualitative and local measurement) by noninvasive probe. Before starting the recording certain conditions are respected: no major effort before the test, the examination room is air-conditioned at a temperature around 30°C and ensure that the patient does not wear clothing or jewelry that may interfere with the recording [13,28-30]. The principle of this technique is to measure the spectral variations of a light reflected by red blood cells and emitted by a helium-neon laser with a wavelength of 632 nm. These variations depend on the speed and number of red blood cells, hematocrit, tissue optic properties and vascular network geometry [31]. Calibration of the device is checked at least once a month. Laser Doppler profile is interpreted independently of the other profiles. Indeed, no threshold or normal value is determined or published. Variations in the endothelial response to acetylcholine injection (Δ ACH) are, therefore, measured and interpreted with reference to baseline, which is the baseline of endothelial changes measured during the first two minutes of the maneuver before any injection of acetylcholine (ACH), 3 successive doses of ACH are injected followed by an increase in local skin temperature. Thus the variations of the endothelial response following the 3 acetylcholine injections and the temperature increase are measured (Δ ACH1, Δ ACH2, Δ ACH3 and Δ Temp) [31].

Statistical analyzes

The statistical analyzes are performed using the Statistica software (Statistica Kamel version 6.0, Stat Soft, France). In a first step and after checking the normal distribution of the studied parameters, we determine the means and the standard deviations of all the quantitative variables (anthropometric and ventilatory) for both G1 and G2 groups of the study. The Mann Whitney U test is used to compare the quantitative variables (endothelial and respiratory parameters) of the two groups. Comparison of categorical variables

(sex-ratio, Smoking habit, hypertension and diabetes...) between groups is set by chi-square test. The degree of significance is set at p lower than 0.05.

Results

Forty eight subjects were included in the study and benefited from the different tests. They were divided into two groups: The G1 group is the control obese group (N=25 with a sex ratio (M/F) = 16/9) and the G2 group is formed of 23 OSAHS patients (sex ratio (M/F) = 16/7). These apneic patients had an Epworth sleepiness score of 13.78 ± 4.92 , an AHI>10 with an oxygen saturation average of $89.30 \pm 6.43\%$ and a number of desaturations per night of sleep at 443.78 ± 147.72 . The G1 group had an AHI<10.

The anthropometric characteristics of the two groups were shown in Table 1, 21 apneic patients and the entire G1 group had obesity and 2 from the G2 group were overweight. The comparison of weight, height and BMI of the two groups did not show a statistically significant difference. The two groups were matched by weight, height, sex and BMI.

Table 1: The anthropometric and clinical characteristics of the two groups of the study.

	Control Group (N=25)	OSAHS Group (N=23)	Total sample (N=48)	P
Sex-ratio (M/F)	16-Sep	16-Jul	32/16	0.682(ns)
Age (yrs)	43.53 \pm 9.60	50.08 \pm 9.28	46.61 \pm 9.92	0.0186 (*)
Weight (Kg)	97.00 \pm 12.93	100.00 \pm 13.20	98.40 \pm 13.01	0.264 (ns)
Height (m)	1.68 \pm 0.09	1.67 \pm 0.09	1.67 \pm 0.09	0.909 (ns)
BMI (Kg/m ²)	34.42 \pm 4.63	35.78 \pm 4.72	35.06 \pm 4.68	0.179 (ns)
Smoking habit (yes/no)	Oct-15	12-Nov	22/26	0.397 (ns)
Diabetes (yes/ no)	Oct-15	Oct-13	20/28	0.807 (ns)
Hypertension (yes/no)	Apr-21	Oct-15	14/34	0.036 (*)

M: Male and F: Female

OSAHS: Obstructive Sleep Apnea Hypopnea Syndrome

BMI: Body Mass Index (Weight (Kg)/Height (m²))

ns: not significant difference between control and OSAHS groups by Mann Whitney U-test

*: p value <0.05, comparison between control and OSAHS groups by Mann Whitney U-test

°: p value<0.05, comparison by chi-square test between control and OSAHS groups of categorical variables (sex-ratio, Smoking habit, Hypertension, Diabetes).

Twenty tow patients (12 from apneic group) were active smokers. The comparison of smoking in both active and passive forms between the two groups showed no significant difference. 14 patients (10 from G2) had an arterial hypertension. 20 patients (10 from G2) had diabetes mellitus (Table 2).

Proximal flows (FEV1; l/s and %) and distal flows (MEF25-75, MEF25, MEF50) values were significantly lower in apneic patients than in controls. Five apneic patients and no one from control group had proximal obstructive ventilatory defect. No significant difference was found between the two groups concerning distal obstructive ventilatory defect (5 from controls and 8 from apneic subjects).

Vital capacity, forced vital capacity and total lung capacity were significantly lower in apneic patients compared to controls. A restrictive ventilatory deficit was present in 26 subjects (16 from apneic group).

Table 2: Respiratory functional characteristics of the two groups of the study: OSAHS group and control group.

	Control Group	OSAHS Group	Total Sample	p
FEV1 (L)	3.26 \pm 0.70	2.59 \pm 0.75	2.95 \pm 0.79	0.005
%FEV1	98.65 \pm 11.86	82.56 \pm 15.30	91.10 \pm 15.70	<0.001
MEF50 (L/s)	4.45 \pm 1.14	3.72 \pm 1.21	4.11 \pm 1.21	0.057
%MEF50	97.76 \pm 22.63	85.263 \pm 26.36	91.89 \pm 25.00	0.057
MEF25 (L/s)	1.43 \pm 0.50	1.20 \pm 0.57	1.33 \pm 0.54	0.217
%MEF25	74.23 \pm 21.81	69.35 \pm 35.28	71.94 \pm 28.71	0.412
MEF25-75 (L/s)	3.51 \pm 0.90	2.99 \pm 0.93	3.26 \pm 0.94	0.062
%MEF25-75	89.30 \pm 19.24	78.95 \pm 26.18	84.45 \pm 23.11	0.138
VC (L)	3.98 \pm 0.90	3.25 \pm 0.96	3.64 \pm 0.99	0.017
%VC	98.11 \pm 14.5	83.01 \pm 12.59	91.03 \pm 15.51	<0.001
FVC (L)	4.00 \pm 0.94	3.14 \pm 1.02	3.60 \pm 1.06	0.006
%FVC	100.42 \pm 13.08	82.61 \pm 14.03	92.06 \pm 16.12	<0.001
FEV1/FVC (%)	82.30 \pm 6.27	79.30 \pm 9.12	80.89 \pm 7.81	0.412
RV (L)	1.66 \pm 0.50	1.65 \pm 0.72	1.66 \pm 0.61	0.525
%RV	89.6 \pm 21.98	83.82 \pm 31.51	86.89 \pm 26.75	0.241
TLC (L)	5.65 \pm 1.21	4.76 \pm 1.28	5.23 \pm 1.31	0.018
%TLC	93.38 \pm 13.70	78.95 \pm 11.91	86.61 \pm 14.69	<0.0001
DLCO (mmol/ KPa/min)	10.70 \pm 2.40	8.70 \pm 2.40	9.800 \pm 2.60	0.008
%DLCO	112.10 \pm 20.20	92.70 \pm 22.00	103.00 \pm 23.00	0.001
FeNO (ppb)	18.40 \pm 9.20	31.30 \pm 13.60	24.85 \pm 11.40	<0.0001

FEV1: Forced Expiratory Volume at the first second (l and %)

VC: Vital Capacity (l and %)

FVC: Forced Vital Capacity (l and %)

FEV1/VC ratio (%)

MEF25-75: Median Maximum Expiratory Flow (l/s and %)

MEF25 and MEF50: Maximum Expiratory Flow at 25 and 50% of FVC (l/s and %)

TLC: Total Lung Capacity (l and %)

RV: Residual Volume (l and %)

DLCO: carbon monoxide transfer capacity (mmol/KPa/min and %)

FeNO: Fraction of Exhaled Nitric Oxide

ns : not significant difference between control and OSAHS groups by Mann Whitney U-test

p of significance, comparison between control and OSAHS groups by Mann Withney U-test.

DLCO and %DLCO were decreased in both groups G1 and G2. 8 from apneic group and 2 from control group had a diffusion abnormality.

The degree of bronchial inflammation, judged by FeNO, was significantly greater in the apneic group than in the control group and was correlated with the degree of severity of OSAHS.

Assessment of vascular endothelial dependent response (VDED) showed a significantly severe VDED dysfunction in all subjects with OSAHS compared to healthy subjects. However, following the rise in temperature, non-vessel-dependent endothelium responses in both groups were comparable. More severe VDED dysfunction in all hypertensive apneic patients compared to non-apneic was significant (Table 3).

Discussion

The main findings of this study were

- OSAHS is characterized by a significant decrease in respiratory function and an increased bronchial inflammation.
- OSAHS altered peripheral and central endothelial function by altering the regulation of endothelial vasomotion.

The group of non-apneic obese was selected from a group of patients who were suspected having OSAHS and whose

Table 3: Parameters of the microcirculation variation in the two groups of the study.

	Control Group	OSAHS Group	Total Sample	p
Δ ACH1	161.5 ± 168.6	66.1 ± 84.3	116.7 ± 142.8	0.006
Δ ACH2	322.8 ± 263.6	129.4 ± 135.2	232 ± 220.9	<0.001
Δ ACH3	442.6 ± 282.4	200.5 ± 189.1	328.8 ± 269.8	0.001
Δ Temp	1161 ± 807.4	728.9 ± 455	958.2 ± 694.2	0.07

ns : not significant difference by Mann Whitney U-test

p of significance, comparison by Mann Withney U-test.

Δ ACH1: variation of the endothelial response following the first dose of acetylcholine.

Δ ACH2: variation of the endothelial response following the second dose of acetylcholine

Δ ACH3: variation of the endothelial response following the third dose of acetylcholine

Δ Temp: variation of the endothelial response following the increase of temperature.

polysomnography or polygraphy did not confirm this diagnosis. Some subjects of this group were selected from an obese, volunteer and healthy group (BMI > 30 kg/m²). This group was used to determine the effect of OSAHS alone on respiratory and cardiovascular functions by comparing apneic obese patients with non-apneic obese subjects. The group of apneic patients was selected after the confirmation of an OSAHS by polysomnography.

All respiratory and vascular functional explorations were performed by the same operator and at the same timing, in the morning for all patients, to respect the reproducibility of the measurements and to avoid circadian variations in respiratory function.

The group of apneic patients (N=23) had a male predominance (16 men) which is often found in the carriers of a SAHOS [8,32-34]. The exact mechanisms of this predisposition were not clear, but it could be explained by an underestimation of the number of women with OSAHS. Indeed, Young et al. [35] estimated that 93% of apneic women were undiagnosed. In addition, male predominance could be related to anatomical factors at upper airways: The increase in neck circumference and the important collapsibility of upper airways in men [36,37]. After menopause, this difference tended to disappear because of the disappearance of the protective hormonal climate of the woman [38]. It has been reported that testosterone increased the collapse of upper airways and that progesterone played a protective role in maintaining good upper airways permeability [39].

The average age of our apneic patients (50 ± 9 years) was comparable to those in the literature. In fact, the majority of patients with OSAHS were older than 50 years [5,12]. These results confirmed the accepted classical notion that the prevalence of OSAHS increased with age [5,12,39,40]. Duran et al. [3] showed that the prevalence of OSAHS increased with age regardless sex with an odds ratio of 2.2 every 10 years. Age-related anatomical and histopathological changes in the pharynx led to increased collapses (loss of elastic tissue) of the upper airways, which may explain the increased prevalence of OSAHS with age [5,38,40]. Indeed, this hypercollapsibility associated to a decrease in muscle tone at upper airways during sleep were responsible for pharyngeal wall vibration and obstructive sleep apnea. Planchard et al. [5] explained the sleep-related respiratory disturbances in apneic elderly patients to the aging of ventilatory control and thoracic mechanical performance.

In this study, all apneic patients were obese with an average BMI of 35.78 Kg/m² ± 4.72 Kg/m². Obesity, especially in its massive or android form, is a major risk factor for OSAHS [15,16]. Indeed a

10% of gain in body weight could predict an increase in AHI of 32%. This modification can be explained by the anatomical modifications of UAW. Obesity is responsible of an increase in the compliance of the pharyngeal walls and the presence of external compression of the pharynx by the peripharyngeal fatty deposits [15,16].

Abdominal fat found in android obesity could also play an important role in sleep apnea [4]. Indeed, since the functional residual capacity is reduced in obese patients, contraction of the diaphragm can cause significant intra-thoracic depression at the beginning of inspiration, which can lead to pharyngeal collapse [36,40].

Spirometric data showed an obstructive ventilator defect in 12 apneic patients and 10 non-apneic obese subjects. The comparison between apneic and non-apneic groups showed a significant difference in FEV1 with lower FEV1 in apneic patients. This could be explained by the rise in oxidative stress during SAHOS leading to a decrease in nitric oxide synthesis by pulmonary tissue and causing bronchial muscles relaxation defect [12,29,41]. However, FEV1 was considered by several authors to be an unsuitable tool for assessing the functional impact of OSAHS since this parameter did not show a significant difference between patients with and without OSAHS during their studies [9,34,42]. MEF25-75, MEF25 and MEF50 are the parameters that provide information on small airway obstruction. However, these parameters depended on the expiratory effort and especially the patient's cooperation, which was often difficult to obtain [11]. In our study, MEF25-75 MEF25 and MEF50 were lower in G2 than in G1. Also Van Meerhaeghe et al. [43] found a significant difference in MEF25-75 between apneic and non-apneic patients. This can be explained by obesity that has resulted in pulmonary restriction with reduced lung volumes and decreased distal flow rates [23,43]. The restrictive ventilator defect was objectified in 10 non-apneic and 16 apneic obese subjects. This restriction could be explained by the consumption of tobacco, especially the narghile, which contains microparticles and heavy metals that can diffuse to the deep lung. This later is often associated to an abnormal DLCO [44]. Morbid obesity is associated with a decrease in static and dynamic lung volumes and an alteration of gas exchange and ventilatory mechanics. The most severe obese patients had a restrictive involvement characterized by a decrease in VC, functional residual capacity (FRC), CPT and RV [41-43]. In our study, VC, FVC, and TLC were significantly different between apneic and obese patients. Apneic patients had higher loss in lung volumes than non-apneic obese. DLCO was significantly lower in apneic group when compared to the control group. This result can be explained in part by bronchial inflammation and endothelial dysfunction. Different from our results, Hoffstein et al. [45] in a study of 1296 apneic patients, found a higher DLCO in apneics. Doré and Orvoën-Frija [21] concluded that apneic or healthy obese patients had an increased in DLCO. In our study, the absence of DLCO elevation could be attributed to the association of two opposite mechanisms occurring during OSAHS: an increase in pulmonary capillary blood volume due to obesity and an increase in cardiac output linked to the hyperactivity of the sympathetic system. These mechanisms tend to increase the DLCO. The alteration of the alveolar-capillary membrane tends to reduce the DLCO. Indeed, during the course of OSAHS, an increase in atherosclerosis and inflammatory manifestations causing an alteration of the pulmonary exchanger was often noted [16,17,46]. The degree of bronchial inflammation, demonstrated by the increase in FeNO values, was significantly greater in the apneic group than the control and correlated with the severity of OSAHS. This increase in FeNO in apneic subjects could be caused by repetitive

apnea, hypoxemia during sleep, and upper airways involvement [29]. In the present study, all patients with OSAHS had lower VDED than non-apneic obese. These results thus confirmed the presence of endothelial dysfunction in subjects with OSAHS compared to healthy obese controls. This dysfunction was present even in the absence of hypertension or other cardiovascular diseases suggesting that OSAHS was an independent risk factor for endothelial dysfunction [29,31,47].

Sanders et al [18] showed the presence of a causal link between OSAHS and endothelial dysfunction. This result may explain in part the pathogenic role of OSAHS in hypertension and cardiovascular disease. In fact, VDED measured after infusion of acetylcholine is decreased in subjects suffering from OSAHS compared to age-matched controls and BMI thus indicating the reduction in nitric oxide bioavailability. Overall, these studies provide direct evidence of the bioavailability of nitric oxide that is reduced in patients with OSAHS with or without cardiovascular disease.

OSAHS negatively affects endothelial regulation of peripheral vasomotricity. This is mainly expressed by the decrease in VDED and is mainly related to a reduction in the bioavailability of nitric oxide, a marker of vascular endothelial function, and an increase in vasoconstrictor substances [13,18,29,47]. Hypoxemia resulting from repeated apneas does not have the same effect on bronchial tissue and vascular endothelium. At the bronchial tree it was responsible of an increase in nitric oxide following inflammation of the bronchial wall (the origin is the bronchial epithelium). At the vascular level this hypoxemia reduced the production of nitric oxide by vascular smooth muscle [29,48]. Several hypotheses were mentioned to explain hypertension in apneics: The sleep fragmentation, intermittent hypoxemia and sympathetic activation were the most validated. Yannoutsos et al. objectified the responsibility of endothelial dysfunction in the occurrence of hypertension [49]. It is well known that OSAHS is associated with notable non-respiratory morbidity, including an elevated prevalence of metabolic syndrome, hypertension, insulin resistance, type 2 diabetes and cardiovascular illnesses, such as transient ischemic attacks, stroke, cardiac arrhythmias, myocardial infarction and pulmonary hypertension [50]. Insulin secretion increases the endogenous release of the potent vasodilator nitric oxide from the endothelium. Circulating exosomes facilitate important intercellular signals that modify endothelial phenotype, and thus emerge as potential fundamental contributors in the context of OSAHS-related endothelial dysfunction [51]. Exosomes may not only provide candidate biomarkers, but are also a likely and plausible mechanism toward OSAHS-induced cardiovascular disease. Recently, it was shown that levels of 8-isoprostane, though not exhaled nitric oxide, distinguish children with OSAHS from those with primary snoring or healthy, correlate with disease severity and closely predict OSAHS in the whole sample observed [52].

In the present study, an evaluation of non-endothelial dependent vasodilatation through local warming was also done. The difference in means between the apneic and non-apneic groups was not significant. Thus, non-endothelial dependent vasodilatation was maintained in apneic patients. These results were comparable to those found in the literature. The vessel diameter in this case was similar in patients with OSAHS and control subjects. Similarly, the percentage increase in vessel diameter in both groups was comparable ($p>0.05$) [53]. In fact the non-endothelial dependent vasodilatation corresponded to the maximum vasodilatation of vessels. It depended on several vascular structures, particularly smooth muscle cells and

C-fibers. It was therefore conceivable that, when a subject had pure endothelial involvement, the non-endothelial mechanisms involved in vasodilatation would be preserved. Thus, the OSAHS represented a vascular risk factor giving pure endothelial dysfunction.

The main limitations of this study were: First, the sample size which was reduced to 48 due to the poor cooperation of patients in performing the respiratory maneuvers. The sample size of this study appeared to be satisfactory compared to that of the literature [32,33]. Second, the study design age and sex matching which should be performed for reducing the risk of bias but it was not performed in this study.

Conclusion

It was confirmed that OSAHS, characterized by a significant decrease in respiratory function and bronchial inflammation, was a disease of the respiratory system. However, an association between OSAHS and cardiovascular involvement was also established. Although the mechanisms underlying this association were not well understood, it was shown that OSAHS altered endothelial function by altering the regulation of endothelial vasomotion (Decreased nitric oxide production at the vascular wall). Thus, measurement of endothelial dysfunction is an early marker of cardiovascular damage related to OSAHS.

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