Research Article

The Ventilatory and Diffusion Dysfunctions in Obese Patients with and without Obstructive Sleep Apnea-Hypopnea Syndrome

Sonia Rouatbi,1,2 Ines Ghannouchi,1,2 Rim Kammoun,1 and Helmi Ben Saad1,2

1Laboratory of Physiology and Explorations, Faculty of Medicine Sousse, University of Sousse, Sousse, Tunisia
2Heart Failure (LR12SP09) Research Laboratory, Farhat Hached Hospital, Sousse, Tunisia

Correspondence should be addressed to Sonia Rouatbi; sonia.rouatbi@gmail.com

Received 2 July 2019; Revised 11 January 2020; Accepted 14 January 2020; Published 10 February 2020

Copyright © 2020 Sonia Rouatbi et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Objective. To analyze the ventilatory and alveolar-capillary diffusion dysfunctions in case of obesity with or without an OSAS.

Methods. It is a cross-sectional study of 48 obese adults (23 OSAS and 25 controls). Anthropometric data (height, weight, and body mass index (BMI)) were collected. All adults responded to a medical questionnaire and underwent polysomnography or sleep polygraphy for apnea-hypopnea index (AHI) and percentage of desaturation measurements. The following lung function data were collected: pulmonary flows and volumes, lung transfer factor for carbon monoxide (DLCO), and fraction of exhaled nitric oxide (FeNO).

Results. Obesity was confirmed for the two groups with a total sample mean value of BMI $\bar{x}$ 35.06 ± 4.68 kg/m². A significant decrease in lung function was noted in patients with OSAS compared with controls. Indeed, when compared with the control group, the OSAS one had a severe restrictive ventilatory defect (total lung capacity: 93 ± 14 vs. 79 ± 12%), an abnormal DLCO (112 ± 20 vs. 93 ± 22%), and higher bronchial inflammation (18.40 ± 9.20 vs. 31.30 ± 13.60 ppb) ($p < 0.05$).

Conclusion. Obesity when associated with OSAS increases the severity of pulmonary function and alveolar-capillary diffusion alteration. This can be explained in part by the alveolar inflammation.

1. Introduction

Obesity has reached epidemic proportions worldwide (12% of the world’s population) [1]. Obesity, vascular dysfunction, and obstructive sleep apnea syndrome (OSAS) are associated disorders. The role of adipocytokines in systemic inflammation and vascular dysfunction has been proved by many studies [2]. Obesity is a risk factor of OSAS, defined as an apnea-hypopnea index (AHI) >10/h [3–6]. OSAS currently represents a real public health problem, with an adult prevalence of 2–4% [4, 6, 7]. Obstructive apnea corresponds to a stop of the naso-oral ventilation with persistence of thoraco-abdominal movements [3–8]. Pharyngeal hyper-collapsibility, often seen in case of obesity, is one of the many causes of OSAS [9]. Polysomnography in the sleep laboratory remains the main tool for diagnosis of OSAS [9–11]. The OSAS can have many serious consequences: metabolic, behavioral, or cardiovascular (coronary insufficiency and hypertension) [8, 9, 12–15]. These latter consequences are common in patients with OSAS, but the underlying mechanisms of this association are unknown. Several hypotheses evoke an alteration of endothelial tissue as a mechanism of these vascular complications in case of OSAS [16]. Thus, the objective of this work is to analyze the ventilatory mechanism and alveolar-capillary diffusion dysfunctions in case of obesity with or without an OSAS.

2. Population and Methods

2.1. Study Design. This was a cross-sectional study conducted in the physiology and functional exploration laboratory. The studied sample was composed of 48 obese adults divided into two groups: an obese control group (G1, n = 25) free from any respiratory disease and an obese OSAS group.
OSAS patients had the following characteristics: age between 20 and 65 years, obesity, and a confirmed OSAS by polysomnography with an AHI ≥ 10. Subjects with one or more of the following criteria were excluded from the study: respiratory infection of the upper or lower respiratory tract, asthmatic disease or chronic obstructive pulmonary disease, known neuromuscular pathology, upper airway abnormality, imperfect performance of required breathing maneuvers, and smoking >10 pack-year [17].

2.2. Survey. All subjects responded to a standardized questionnaire seeking inclusion and noninclusion criteria, respiratory function signs (cough, dyspnea, expectoration, snoring, and daytime sleepiness), and anthropometric data (sex, age (years), weight (kg), height (m), and body mass index (BMI, kg/m²)). Based on BMI values, three classes of obesity were defined [18, 19]: class 1 (BMI between 30 and 34.9 kg/m²), class 2 (BMI between 35 and 39.9 kg/m²), and class 3 (BMI greater than 40 kg/m²).

2.3. Functional Respiratory Explorations: Total Body Plethysmography. Total body plethysmography was performed for all participants in the study using a plethysmograph (ZAN 500, Messgeraete GmbH2000, Germany). Ventilatory data were interpreted according to the international recommendations [20]. The total body plethysmography allows the realization of a flow-volume curve and the measurement of ventilatory flows and pulmonary volumes. The measured data were the following: forced expiratory volume at the first second (FEV₁, l), slow vital capacity (SVC, l), forced vital capacity (FVC, l), FEV₁/FVC ratio (%), maximal mid-expiratory flow (MMEF, l/s), forced expiratory flow at 50% of FVC (FEF50%, l/s), total lung capacity (TLC, l), and residual volume (RV, l). These data were considered diminished when they were below the lower limit of normal (LLN). The LLNs were determined from the specific reference values of the Tunisian population. Different ventilatory patterns were defined: (i) a proximal obstructive ventilatory defect is defined when the FEV₁/VC or FEV₁/FVC ratios were lower than the LLN [20]; (ii) a distal obstructive ventilatory defect is defined when the FEV₁/FVC ratio is normal, the FVC is normal, and FEF25% or FEF50%, or MMEF were less than the LLN [20]; (iii) a TLC lower than the LLN defines a restrictive ventilatory defect [20].

2.4. Carbon Monoxide Transfer Capacity (DLCO). DLCO (mmol/KPa/min) was measured by the inspiratory apnea method. These data are considered diminished when they are lower than the LLN [20].

2.5. Polysomnography. 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 [3, 5, 8]. Hypopneas are defined as a reduction of more than 50% of the oro-nasal flow amplitude during 10 seconds, accompanied by 3% desaturation and/or arousal. The AHI is the number of apneas and hypopneas per hour of sleep [21, 22]. The severity of OSAS is defined according to the value of AHI [3, 5]: light (AHI < 15), moderate (15 < AHI < 30), and severe (AHI > 30) [23]. Polysomnographic scoring and staging were based on Rechtschaffen and Kales study, and episodes of arousals were assessed according to the guidelines in the previous studies [24].

2.6. Measurement of Exhaled Fraction of Nitric Oxide (FNO). FNO was measured by the Medisoft HypAir method using an electrochemical analyzer (Medisoft, Sorinnes, Belgium). It was based on the chemiluminescence method [25]. The instrument was calibrated and used according to the manufacturer’s instructions. The measurement of FNO was made following the international recommendations [25]. Three acceptable measurements were taken at a flow rate of 50 ml/s at 15 minutes as recommended [25]. The average of the three values was used. FNO was expressed in parts per billion (ppb), which is the equivalent of nanoliter per liter [25].

2.7. Statistical Analysis. The statistical analysis was 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 data, the means (standard deviations) of all the quantitative data (anthropometric and ventilatory) for both groups were determined. The Mann–Whitney U test was used to compare the quantitative data (respiratory data) of the two groups. Comparison of categorical data (sex-ratio, smoking habits, hypertension, diabetes, and so on) between the two groups was set by the chi-squared test. The degree of significance was set at “p” lower than 0.05.

3. Results

Forty-eight participants were included in the study. They were divided into two groups: G₁ (25 obese controls, 16 males) and G₂ (23 obese OSAS, 16 males). The OSAS patients had an Epworth sleepiness score of 13.78 ± 4.92, an AHI > 10 with an oxygen saturation average of 89 ± 6%, and a number of desaturations per night of sleep at 443 ± 148. The G₁ group had an AHI < 10.

The anthropometric data of the two groups are shown in Table 1. Twenty-one OSAS patients and the entire G₁ group had obesity, and two OSAS patients were overweight. The two groups were matched for weight, height, sex, and BMI. Twenty-tow participants (12 from the OSAS group) were active smokers. The comparison of smoking habits between the two groups showed no significant difference. Fourteen participants (10 from the OSAS group) had an arterial hypertension. Twenty participants (10 the OSAS group) had diabetes mellitus. Table 2 summarizes the respiratory functional data of the two groups.

A significant decrease in lung function was noted in patients with OSAS compared with controls. Proximal (FEV₁ expressed in liters and in percentage) and distal
The group of nonapneic obese was selected from a group of participants who were suspected having OSAS and whose polysomnography or polygraphy did not confirm this diagnosis. This group was used to determine the effect of OSAS alone on respiratory and cardiovascular functions by comparing OSAS obese patients with nonOSAS obese participants.

The OSAS group was selected after the confirmation of OSAS by polysomnography. All respiratory and vascular explorations were performed by the same operator and at the same timing, in the morning for all participants, to respect the reproducibility of the measurements.

4. Discussion

This study showed that obesity when associated to OSAS increased the risk of altered pulmonary function with a decrease in DLCO. This result can be explained by both alveolar inflammation (increased F\textsubscript{2}NO) and vascular dysfunction.

### Table 1: Anthropometric and clinical characteristics of the two obese groups.

|                      | Control group (n = 25) | OSAS group (n = 23) | Total sample (n = 48) | p       |
|----------------------|------------------------|---------------------|-----------------------|---------|
| Male (number)        | 16                     | 16                  | 32                    | 0.682 (ns) |
| Age (years)          | 43.53 $\pm$ 6.60       | 50.08 $\pm$ 9.28    | 46.61 $\pm$ 9.92      | 0.019 * |
| 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) |
| Body mass index (kg/m\textsuperscript{2}) | 34.42 $\pm$ 4.63       | 35.78 $\pm$ 4.72    | 35.06 $\pm$ 4.68      | 0.179 (ns) |
| Smoking habits (yes/no) | 10/15                 | 12/11               | 22/26                 | 0.397 (ns) |
| Diabetes mellitus (yes/no) | 10/15                 | 10/13               | 20/28                 | 0.807 (ns) |
| Arterial hypertension (yes/no) | 4/21                  | 10/15               | 14/34                 | 0.036 ♠ |

ns, not significant difference; OSAS, obstructive sleep apnea syndrome. ♠ p value < 0.05: comparison between controls and OSAS groups by the Mann–Whitney U test. ♠ p value < 0.05: comparison between controls and OSAS groups by the chi-squared test.

### Table 2: Respiratory functional data of the two obese groups.

|                      | Control group (n = 25) | OSAS group (n = 23) | Total sample (n = 48) | p       |
|----------------------|------------------------|---------------------|-----------------------|---------|
| FEV\textsubscript{1} (L) | 3.26 $\pm$ 0.70        | 2.59 $\pm$ 0.75     | 2.95 $\pm$ 0.79       | 0.005   |
| FEV\textsubscript{1} (%) | 99 $\pm$ 12            | 83 $\pm$ 15         | 91 $\pm$ 16           | <0.001  |
| FEF\textsubscript{50%} (L/s) | 4.45 $\pm$ 1.14        | 3.72 $\pm$ 1.21     | 4.11 $\pm$ 1.21       | 0.057   |
| FEF\textsubscript{50%} (%) | 98 $\pm$ 23            | 85 $\pm$ 26         | 92 $\pm$ 25           | 0.057   |
| FEF\textsubscript{25%} (L/s) | 1.43 $\pm$ 0.50        | 1.20 $\pm$ 0.57     | 1.33 $\pm$ 0.54       | 0.217   |
| FEF\textsubscript{25%} (%) | 74 $\pm$ 22            | 69 $\pm$ 35         | 72 $\pm$ 29           | 0.412   |
| MMEF (L)             | 3.51 $\pm$ 0.90        | 2.99 $\pm$ 0.93     | 3.26 $\pm$ 0.94       | 0.062   |
| MMEF (%)             | 89 $\pm$ 19            | 79 $\pm$ 26         | 84 $\pm$ 23           | 0.138   |
| SVC (L)              | 3.98 $\pm$ 0.90        | 3.25 $\pm$ 0.96     | 3.64 $\pm$ 0.99       | 0.017   |
| SVC (%)              | 98 $\pm$ 14            | 83 $\pm$ 12         | 91 $\pm$ 16           | <0.001  |
| FVC (L)              | 4.00 $\pm$ 0.94        | 3.14 $\pm$ 1.02     | 3.60 $\pm$ 1.06       | 0.006   |
| FVC (%)              | 100 $\pm$ 13           | 83 $\pm$ 14         | 92 $\pm$ 16           | <0.001  |
| FEV\textsubscript{1}/FVC (%) | 82 $\pm$ 6.4         | 79 $\pm$ 9          | 81 $\pm$ 8            | 0.412   |
| RV (L)               | 1.66 $\pm$ 0.50        | 1.65 $\pm$ 0.72     | 1.66 $\pm$ 0.61       | 0.525   |
| RV (%)               | 90 $\pm$ 22            | 84 $\pm$ 32         | 87 $\pm$ 27           | 0.241   |
| TLC (L)              | 5.65 $\pm$ 1.21        | 4.76 $\pm$ 1.28     | 5.23 $\pm$ 1.31       | 0.018   |
| TLC (%)              | 93 $\pm$ 14            | 79 $\pm$ 12         | 87 $\pm$ 15           | <0.0001 |
| DLCO (mmol/KPa/min)   | 10.70 $\pm$ 2.40       | 8.70 $\pm$ 2.40     | 9.80 $\pm$ 2.60       | 0.008   |
| DLCO (%)             | 112 $\pm$ 20           | 93 $\pm$ 22         | 103 $\pm$ 23          | 0.001   |
| F\textsubscript{2}NO (ppb) | 18.40 $\pm$ 9.20       | 31.30 $\pm$ 13.60   | 24.85 $\pm$ 11.40     | <0.0001 |

DLCO, carbon monoxide transfer capacity; FEF\textsubscript{50%}, forced expiratory flow at 50% of FVC; F\textsubscript{2}NO, fraction of exhaled nitric oxide; FEV\textsubscript{1}, forced expiratory volume at the first second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; ns, not significant difference; RV, residual volume; SVC, slow vital capacity; TLC, total lung capacity; %, percentage of predicted value; p, comparison between controls and OSAS groups by the Mann–Whitney U test.
tended to disappear because of the disappearance of the protective hormonal climate of the female [32]. It has been reported that testosterone increased the collapse of upper airways and that progesterone played a protective role in maintaining good upper airway permeability [33].

The average age of the OSAS patients was 50 ± 9 years. In fact, the majority of patients with OSAS were older than 50 years [7, 34]. These results confirmed the accepted classical notion that the prevalence of OSAS increased with age [7, 33, 35, 36]. Durán et al. [5] showed that the prevalence of OSAS 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 the increased collapses (loss of elastic tissue) of the upper airways, which may explain the increased prevalence of OSAS with age [7, 32, 36]. Indeed, this hypercollapsibility associated to a decrease in muscle tone at upper airways during sleep was responsible for pharyngeal wall vibration and OSAS [36]. Planchard et al. [7] explained the sleep-related respiratory disturbances in apneic elderly patients to the aging of the ventilatory control and the thoracic mechanical performance.

In this study, all OSAS patients were obese with an average BMI of 35.78 ± 4.72 kg/m². Obesity, especially in its massive or android form, is a major risk factor for OSAS [13, 14]. 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 upper airways. 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 [13, 14]. Abdominal fat found in android obesity could also play an important role in OSAS [4]. Indeed, since the functional residual capacity (FRC) is reduced in obese patients, contraction of the diaphragm can cause significant intrathoracic depression at the beginning of inspiration, which can lead to pharyngeal collapse [30, 36].

Spirometric data showed an obstructive ventilatory defect in 12 obese OSAS patients and 10 obese controls. The comparison between OSAS and control groups showed a significant lower FEV₁ (L and %) in the OSAS group. This could be explained by the rise in oxidative stress during OSAS leading to a decrease in NO synthesis by pulmonary tissue and causing bronchial muscles relaxation defect [34, 37, 38]. However, FEV₁ was considered by several authors to be an unsuitable tool for assessing the functional impact of OSAS since these data did not show a significant difference between participants with and without OSAS during their studies [11, 28, 39]. MMEF, FEF₂₅/₇₅, and FEF₅₀ are the data that provide information on small airway obstruction. However, these data depended on the expiratory effort and especially the participants’ cooperation, which was often difficult to obtain [20]. In the present study, MMEF, FEF₂₅/₇₅, and FEF₅₀ were lower in the obese OSAS patients than in the obese controls. This can be explained by obesity that reduced lung volumes by pulmonary restriction and so decreased distal flow rates [21]. The restrictive ventilatory defect was objectified in 10 controls and 16 OSAS. 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 SVC, FRC, TLC, and RV [38, 39]. In the present study, SVC, FVC, and TLC were significantly lower in the OSAS group than the control one. DLCO was significantly lower in the OSAS group when compared with the control group. This result can be explained in part by bronchial inflammation and endothelial dysfunction. Different from our results, Hoffstein and Oliver [40] found a higher DLCO in 1296 apneic patients. Doré and Orvoën-Frijia [19] concluded that apneic or obese nonapneic patients had an increased DLCO. In this study, the absence of DLCO elevation could be attributed to the association of two opposite mechanisms occurring during OSAS: (i) an increase in pulmonary capillary blood volume due to obesity and an increase in cardiac output linked to the hyperactivity of the sympathetic system, this latter tends to increase the DLCO; (ii) an alteration of the alveolar-capillary membrane which tends to reduce the DLCO. Indeed, during the course of OSAS in obese patients, an increase in the atherosclerosis and the inflammatory manifestations causing an alteration of the pulmonary exchanger was often noted [14, 15, 41]. The degree of bronchial inflammation was significantly greater in the OSAS group than the control group. The Fₑ NO value correlated with the severity of OSAS. This increase in Fₑ NO in obese OSAS could be caused by repetitive apnea and hypoxemia during sleep [37].

In the present study, arterial hypertension is significantly more frequent in the OSAS group than the obese control group. Many studies provide direct evidence of the bioavailability of NO that is reduced in OSAS patients with or without cardiovascular diseases. OSAS negatively affects endothelial regulation of peripheral vasmotoricity [12, 16, 37, 42]. 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 NO following inflammation of the bronchial wall (the origin is the bronchial epithelium). At the vascular level, this hypoxemia reduced the production of NO by vascular smooth muscle [37, 43]. Several hypotheses were advanced to explain hypertension in apneics: sleep fragmentation, intermittent hypoxemia, and sympathetic activation were the most validated. Yanoutsos et al. [44] objectified the responsibility of endothelial dysfunction in the occurrence of hypertension. It is well known that OSAS is associated with notable nonrespiratory morbidity, including an elevated prevalence of metabolic syndrome, arterial hypertension, insulin resistance, type 2 diabetes, and cardiovascular illnesses, such as transient ischemic attacks, stroke, cardiac arrhythmias, myocardial infarction, and pulmonary hypertension [45]. Insulin secretion increases the endogenous release of the potent vasodilator NO from the endothelium [45]. Circulating exosomes facilitate important intercellular signals that modify endothelial phenotype and thus emerge as potential fundamental contributors in the context of OSAS-related endothelial dysfunction [46]. Exosomes may not only provide candidate biomarkers but are also a
likely and plausible mechanism toward OSAS-induced cardiovascular disease [46]. Recently, it was shown that levels of 8-isoprostane, though not exhaled NO, distinguish children with OSAS from those with primary snoring or healthy, correlate with disease severity, and closely predict OSAS in the whole sample observed [47].

This study presents some limitations: first, the sample size which was reduced to 48 due to the poor cooperation of participants in performing the respiratory maneuvers; the sample size of this study appeared to be satisfactory compared with that noted in the literature [26, 27].

5. Conclusion

It is confirmed that obesity and OSAS are, when associated, a major risk factor to decreased ventilation and diffusion lung functions with a trend to bronchial inflammation.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] K. M. Flegal, B. K. Kit, H. Orpana, and B. I. Graubard, “Association of all-cause mortality with overweight and obesity using standard body mass index categories,” JAMA, vol. 309, no. 1, pp. 71–82, 2013.

[2] J. Van de Voorde, B. Pauwels, C. Boydens, and K. Decaluwe, “Adipokytokines in relation to cardiovascular disease,” Metabolism, vol. 62, no. 11, pp. 1513–1521, 2013.

[3] A. Lurie, “Obstructive sleep apnea in adults: epidemiology, clinical presentation, and treatment options,” Advances in Cardiology, vol. 46, pp. 1–42, 2011.

[4] R. H. Goodday, D. S. Percious, A. D. Morrison, and C. G. Robertson, “Obstructive sleep apnea syndrome: diagnosis and management,” Journal (Canadian Dental Association), vol. 67, no. 11, pp. 652–658, 2001.

[5] J. Durán, S. Esnaola, R. Rubio, and Á. Iztueta, “Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr,” American Journal of Respiratory and Critical Care Medicine, vol. 163, no. 3, pp. 685–689, 2001.

[6] T. Young, M. Palta, J. Dempsey, J. Skatrud, S. Weber, and S. Badr, “The occurrence of sleep-disordered breathing among middle-aged adults,” New England Journal of Medicine, vol. 328, no. 17, pp. 1230–1235, 1993.

[7] D. Planchard, F. Moreau, J. Paquerelle, J.-P. Neau, and J.-C. Meurice, “Sleep apnea syndrome in the elderly,” Revue des Maladies Respiratoires, vol. 20, no. 4, pp. 558–565, 2003.

[8] P. C. Deegan and W. T. McNicholas, “Pathophysiology of obstructive sleep apnoea,” European Respiratory Journal, vol. 8, no. 7, pp. 1161–1178, 1995.

[9] U. Seneviratne and K. Puvanendran, “Excessive daytime sleepiness in obstructive sleep apnea: prevalence, severity, and predictors,” Sleep Medicine, vol. 5, no. 4, pp. 339–343, 2004.

[10] F. Zerah-Lancner, F. Lofaso, M. P. D’ortho et al., “Predictive value of pulmonary function parameters for sleep apnea syndrome,” American Journal of Respiratory and Critical Care Medicine, vol. 162, no. 6, pp. 2208–2212, 2000.

[11] A. Van Eyck, K. Van Hoorenbeeck, B. Y. De Winter, L. Van Gaal, W. De Backer, and S. L. Verhulst, “Sleep-disordered breathing and pulmonary function in obese children and adolescents,” Sleep Medicine, vol. 15, no. 8, pp. 929–933, 2014.

[12] C. E. Korcarz, J. H. Stein, P. E. Peppard, T. B. Young, J. H. Barnet, and F. J. Nieto, “Combined effects of sleep disordered breathing and metabolic syndrome on endothelial function: the Wisconsin Sleep Cohort study,” Sleep, vol. 37, no. 10, pp. 1707–1713, 2014.

[13] Y. Toyama, K. Tanizawa, T. Kubo et al., “Impact of obstructive sleep apnea on liver fat accumulation according to sex and visceral obesity,” PLoS One, vol. 10, no. 6, Article ID e0129513, 2015.

[14] L. F. Drager, S. M. Togei, V. Y. Polotsky, and G. Lorenzi-Filho, “Obstructive sleep apnea,” Journal of the American College of Cardiology, vol. 62, no. 7, pp. 569–576, 2013.

[15] C. Costa, B. Santos, D. Severino et al., “Obstructive sleep apnea syndrome: an important piece in the puzzle of cardiovascular risk factors,” Clínica e Investigación en Arteriosclerosis, vol. 27, no. 5, pp. 256–263, 2014.

[16] M. H. Sanders, “article reviewed: impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea,” Sleep Medicine, vol. 2, no. 3, pp. 267–268, 2001.

[17] P. L. Enright, R. A. Kronmal, M. Higgins, M. Schenker, and E. F. Haponik, “Spirometry reference values for women and men 65 to 85 Years of age: cardiovascular health study,” American Review of Respiratory Disease, vol. 147, no. 1, pp. 125–133, 1993.

[18] E. E. Calle, M. J. Thun, J. M. Petrelli, C. Rodriguez, and C. W. Heath, “Body-mass index and mortality in a prospective cohort of U.S. adults,” New England Journal of Medicine, vol. 341, no. 15, pp. 1097–1105, 1999.

[19] M. F. Doré and E. Orvoën-Frija, “Respiratory function in the obese subject,” Revue de Pneumologie Clinique, vol. 58, no. 2, pp. 73–81, 2002.

[20] R. Pellegrino, G. Vegi, V. Brusasco et al., “Interpretative strategies for lung function tests,” European Respiratory Journal, vol. 26, no. 5, pp. 948–968, 2005.

[21] R. J. Kimoff, E. Sforza, V. Champagne, L. Ofiara, and D. Gendron, “Upper airway sensation in snoring and obstructive sleep apnea,” American Journal of Respiratory and Critical Care Medicine, vol. 164, no. 2, pp. 250–255, 2001.

[22] W. H. Tsai, W. W. Flemons, W. A. Whitelaw, and J. E. Remmers, “A comparison of apnea-hypopnea indices derived from different definitions of hypopnea,” American Journal of Respiratory and Critical Care Medicine, vol. 159, no. 1, pp. 43–48, 1999.

[23] L. J. Epstein, D. Kristo, P. J. Strollo Jr. et al., “Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults,” Journal of Clinical Sleep Medicine, vol. 5, no. 3, pp. 263–276, 2009.

[24] A. Rechtschaffen and A. Kales, A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects, US Government Printing Office, US Public Health Service, Washington, DC, USA, 1968.

[25] American Thoracic Society and European Respiratory Society, “ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005,” American Journal of Respiratory and Critical Care Medicine, vol. 162, no. 6, pp. 2208–2212, 2000.
[26] M. Bonay, A. Nitenberg, and D. Maillard, “Should flow-volume loop be monitored in sleep apnea patients treated with continuous positive airway pressure?,” *Respiratory Medicine*, vol. 97, no. 7, pp. 830–834, 2003.

[27] Y. Tun, W. Hida, S. Okabe et al., “Inspiratory effort sensation to added resistive loading in patients with obstructive sleep apnea,” *Chest*, vol. 118, no. 5, pp. 1332–1338, 2000.

[28] F. Shirato, F. Lofaso, A. Coste, F. Ricolfi, F. Goldenberg, and A. Harf, “Pulmonary function in obese snorers with or without sleep apnea syndrome,” *American Journal of Respiratory and Critical Care Medicine*, vol. 156, no. 2, pp. 522–527, 1997.

[29] T. Young, L. Evans, L. Finn, and M. Palta, “Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women,” *Sleep*, vol. 20, no. 9, pp. 705–706, 1997.

[30] V. Mohsenin, “Effects of gender on upper airway collapsibility and severity of obstructive sleep apnea,” *Sleep Medicine*, vol. 4, no. 6, pp. 523–529, 2003.

[31] L. J. Brooks and K. P. Strohl, “Size and mechanical properties of the pharynx in healthy men and women,” *American Review of Respiratory Disease*, vol. 146, no. 6, pp. 1394–1397, 1992.

[32] A. T. Whittle, I. Marshall, I. L. Mortimore, P. K. Wraith, R. J. Sellar, and N. J. Douglas, “Neck soft tissue and fat distribution: comparison between normal men and women by magnetic resonance imaging,” *Thorax*, vol. 54, no. 4, pp. 323–328, 1999.

[33] O. Resta, P. Bonfitto, R. Sabato, G. De Pergola, and M. P. F. Barbaro, “Prevalence of obstructive sleep apnoea in a sample of obese women: effect of menopause,” *Diabetes, Nutrition & Metabolism*, vol. 17, no. 5, pp. 296–303, 2004.

[34] K. A. Griffith, D. L. Sherrill, E. M. Siegel, T. A. Manolio, H. W. Bonekat, and P. L. Enright, “Predictors of loss of lung function in the elderly,” *American Journal of Respiratory and Critical Care Medicine*, vol. 163, no. 1, pp. 61–68, 2001.

[35] M. Ashraf, S. A. Shaffi, and A. S. BaHammam, “Spirometry sample of obese women: effect of menopause,” *American Journal of Respiratory and Critical Care Medicine*, vol. 171, no. 6, pp. 523–528, 2005.

[36] A. Malhotra, Y. Huang, R. Fogel et al., “Aging influences on the Turkish Society of Cardiology, vol. 43, no. 4, pp. 333–339, 2015.

[37] A. Carreras, S. X. Zhang, E. Peris et al., “Chronic sleep fragmentation induces endothelial dysfunction and structural vascular changes in mice,” *Sleep*, vol. 37, no. 11, pp. 1817–1824, 2014.

[38] N. Glas, J.-M. Vergnon, and Y. Pacheco, “Intérêt des méthodes non invasives d’évaluation de l’inflammation bronchique dans l’asthme,” *Revue de Pneumologie Clinique*, vol. 69, no. 2, pp. 76–82, 2013.

[39] G. Tarantino, V. Citro, and C. Finelli, "What non-alcoholic fatty liver disease has got to do with obstructive sleep apnoea syndrome and vice versa?" *Journal of Gastrointestinal and Liver Diseases*, vol. 23, no. 3, pp. 291–299, 2014.

[40] R. Bhattacharjee, A. Khalyfa, A. A. Khalyfa et al., "Exosomal cargo properties, endothelial function and treatment of obesity hypoventilation syndrome: a proof of concept study," *Journal of Clinical Sleep Medicine*, vol. 14, no. 5, pp. 797–807, 2018.

[41] M. Barreto, P. Montusch, M. Evangelisti et al., “Comparison of two exhaled biomarkers in children with and without sleep disordered breathing,” *Sleep Medicine*, vol. 45, pp. 83–88, 2018.