Clinical Characteristics of Patients with Very Severe Obstructive Sleep Apnea

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Abstract

Introduction: The presence of obstructive sleep apneas (OSA) is a prevalent disease, whose severity is determined from the Apnea-Hypopnea Index (AHI). Very severe OSA (vsOSA) is defined by an AHI $\geq$ 60 events/hour; with clinical characteristics that could be different. The purpose of this study was to describe the clinical characteristics of patients with sOSA and compare them with less severe manifestations of this disease.

Materials and Methods: Retrospective study of patients referred to a specialized hypertension center who met clinical criteria for the study of OSA. Patients were analyzed by means of a respiratory polygraphy, Ambulatory Monitoring of Arterial Pressure (AMAP), questionnaires and laboratory tests. We used non-parametric tests for the analysis of the results.

Results: Of the 115 patients with OSA included in the study, 57 showed moderate OSA (mOSA), 48 sOSA and 10 vsOSA. No statistically significant differences were observed in age, Body Mass Index (BMI), glycemia, percentage of diabetic patients, or waist or neck diameter. We observed that the proportion of patients with arterial hypertension became higher as the severity of the OSA increased. This increase was significant only regarding the value of diastolic arterial pressure in very severe patients (vsOSA: 94.0 $\pm$ 7.7 mmHg vs. sOSA: 87.9 $\pm$ 8.7 mmHg and mOSA: 84.4 $\pm$ 8.2 mmHg; $p < 0.05$ and $p < 0.01$, respectively).

Conclusions: In agreement with previous studies, our patients with vsOSA showed a higher degree of diastolic hypertension with clinical characteristics similar to less severe manifestations of OSA.

Key words: Obstructive sleep apneas-hypopneas, Apnea-hypopnea index, Arterial hypertension

Introduction

The obstructive sleep apnea-hypopnea syndrome (OSAHS) is a disease whose diagnostic criteria are determined by the presence of an apnea-hypopnea index (AHI) of more than 5 events/hour associated with excessive daytime somnolence or with heart or metabolic disease. Its prevalence in Latin America is estimated to be around 28% in middle-aged individuals[1]. In Latin America, in a study performed in the metropolitan area of Sao Paulo (Brazil), Tufik et al describe a prevalence of around 32.8%[2] in the general population[2].

The presence of obstructive sleep apneas (OSAs) is a risk factor related to arterial hypertension, coronary heart disease and stroke[3-5]. Different mechanisms might seem to be related to the develop-

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ment of complications to this disease, including oxidative stress and inflammation[6]. Cohort studies have shown that weight gain increases the risk to develop OSA[7, 8].

The severity of the OSA is determined by the frequency in which apneas or hypopneas are produced, expressed as the number of events per hour (AHI) or as Respiratory Event Related Arousals (RERAs). With these values, severity can be grouped as: mild OSA (5 > AHI < 15 events/hour), moderate OSA (15 > AHI < 30) or severe OSA (AHI > 30)[9, 10]. However, the categorization of "very severe obstructive sleep apnea (vsOSA)" is relatively unusual and we still don´t know all of its characteristics in detail. Recent publications have started to describe the clinical particularities of this population. Jurcevic et al have suggested that patients with AHI ≥ 60 events/hour would show a significant increase in mortality[11]. On the other hand, a case-control study in patients with AHI ≥ 100 events/hour would indicate that this increase in the severity up to values of more than 100 events/hour would be related to the increase in the neck circumference and the presence of arterial hypertension[12].

The purpose of this study was to describe clinical and biochemical characteristics of patients with very severe OSA referred to the Arterial Hypertension Center of the Hospital Británico de Buenos Aires selected for an ambulatory sleep study for clinical suspicion of OSA.

Materials and methods

Design
Retrospective study to describe patients ≥ 18 years old referred to a specialized arterial hypertension center for the evaluation of cardiovascular risk factors between September, 2015 and March, 2017. We included those patients who showed an increased risk of developing OSA. This study was approved by the Institutional Review Board of the Hospital Británico in accordance with the Helsinki rules. All the patients signed an informed consent.

Population
We included consecutive patients between 18 and 80 years old, evaluated for the diagnosis or follow-up of arterial hypertension who obtained 5 or more points in the STOP-BANG[11] questionnaire; an Epworth Sleepiness Scale (ESS) value of more than 10 or high risk, according to the Berlin scale. We carried out a metabolic evaluation and an ambulatory sleep study (self-administered respiratory polygraphy) including only those patients with an AHI ≥ 15 in the Respiratory Polygraphy (RP). We excluded patients with symptomatic heart failure, neuromuscular diseases, known diagnosis of COPD (chronic obstructive pulmonary disease), use of CPAP (Continuous Positive Airway Pressure) or some modality of ventilatory support or supplemental oxygen.

Recorded clinical parameters
Arterial pressure (AP): the measurement of the AP was recorded with an automatic tensiometer (OMRON 7220). After 5 minutes at rest, three measurements were made, separated by 2 minutes, and the average was recorded. 24-hour Ambulatory Monitoring of Arterial Pressure (AMAP) was carried out with Spacelabs Ultralite© equipment (model 90217, SpaceLabs, Redmond, WA). The AP measurements were set every 15 minutes during the day (8:00 a.m. to 11:00 p.m.) and every 30 minutes during the night (11:00 p.m. to 8:00 a.m.). Normotension is defined as day and night AP values less than or equal to 135/85 mmHg and 120/70 mmHg, respectively. The AHT (arterial hypertension) diagnosis was confirmed after the analysis of the Ambulatory Monitoring of Arterial Pressure (AMAP), classifying arterial hypertension as: systolic, diastolic or systo-diastolic. The RP and the AMAP were recorded on successive nights.

Biochemical Parameters: Venous blood samples were obtained under fasting conditions the morning before the RP in order to determine glucose, triglycerides (TGL), total cholesterol and HDL (high-density lipoprotein) cholesterol levels. These values were determined by standard enzymatic methods in an Abbott ci8200© analyzer (Abbott, Abbott Park, Illinois, USA).

Questionnaires**:** All the participants systematically completed the questionnaires, validated in the Spanish language: Berlin questionnaire[13], Epworth Subjective Sleepiness Scale (ESS)[14] and STOP-BANG Questionnaire (SBQ)[15-17].

Self-administered home-based respiratory polygraphy: we used Apnea Link Air© (ResMed. Australia) polygraphs with five channels and three basic signals, pulse oximetry, nasal cannula flow and thoracic effort (level III devices of the American Academy of Sleep Medicine)[18]. We considered as valid those measurements with a total recording time with manual analysis of > 4 hours. Apnea was defined as reduction of airflow of > 80% of the basal $\geq$ 10 seconds (s), and hypopneas were considered as a reduction of airflow of 50% $\geq$ 10 s associated with desaturations $\geq$ 3%[19].

The AHI was defined as the number of respiratory events (apneas or hipopneas) per recording hour. The Oxygen Desaturation Index (ODI) was equally calculated over the total recording time, and the T90 was considered in percentage of valid TRT. The ODI was defined according to the 3% desaturation criterion regarding the immediately preceding baseline value, and the same severity categories of the AHI were defined (normal (AHI < 5/h), mild (AHI between 6 and 14.9 events per hour), moderate (AHI between 15 and 29.9/hour), severe (AHI $\geq$ 30/hour) and very severe (AHI $\geq$ 60/hour).

Statistical Analysis

Patients were grouped by severity categories, according to their AHI value. Thus, patients were grouped as very severe OSA (vsOSA) with an AHI $\geq$ 60 events/hour; severe OSA (sOSA) with an AHI between 30 and 59.9 and moderate OSA (mOSA) with an AHI between 15 and 29.9. The results were expressed as mean and standard deviation or median and interquartile ranges, depending on data distribution. The groups were compared using the ANOVA test, the Kruskal Wallis multiple comparison test for continuous variables, and the Fisher test for qualitative variables. The value of p < 0.05 was considered significant.

Results

We included in the study 115 patients with OSA: 57 showed moderate OSA, 48 severe OSA and 10 very severe OSA (**Figure 1**).

Diagram of patient selection
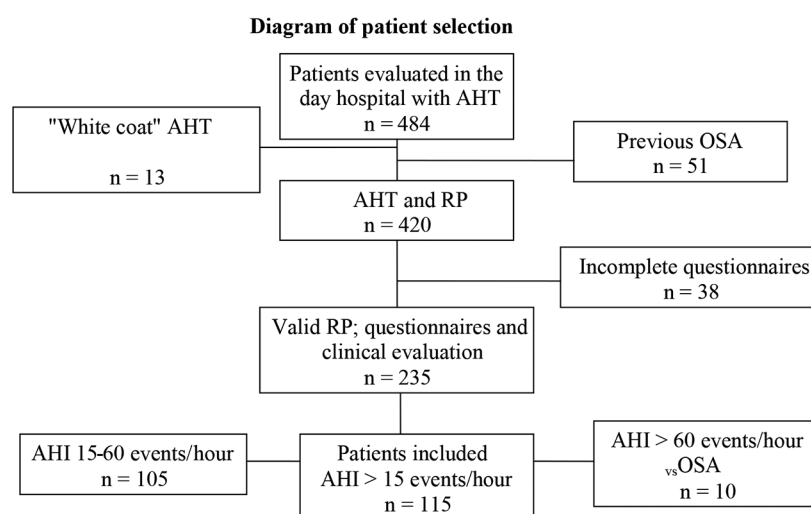
Figure 1. Diagram of patient selection in the day hospital evaluation.

As can be observed in **Table 1**, most of the patients were middle-aged men (86.9%), with confirmed diagnosis of hypertension. No differences were observed regarding the Body Mass Index (BMI), waist perimeter or neck circumference among the 3 groups under analysis. Further, no differences were observed among parameters such as glycemia, HDL, TGL or percentage of patients with diabetes. However, we did observe a statistically significant reduction in hematocrit and hemoglobin levels in patients with very severe OSA, in comparison with severe and moderate OSA (hematocrit %: 39.3 ± 2.1 vs. 41.9 ± 3.1 and 43.1 ± 3.1; $p < 0.05$ and $p < 0.01$ respectively and hemoglobin (g/dL): 13.1 ± 0.7 vs. 14.2 ± 1.2 and 14.6 ± 1.1; $p < 0.05$ and $p < 0.01$ respectively), **Figure 2 A and B.**

**TABLE 1.** Demographic characteristics of patients grouped according to severity of OSA

	Very severe OSA	Severe OSA	Moderate OSA	p
N	10	48	57	
Age	52.5 (41.0-61.0)	56.5 (45.0-63.7)	60.0 (54.2-59.1)	0.06
% Men	90.0	89.5	82.4	0.53
BMI (kg/m2)	30.7 (24.4-37.4)	31.3 (21.4-34.7)	29.7 (24.9-34.3)	0.23
Waist (cm)	116.5 (104.5-138.5)	118.0 (106.0-128.0)	100.0 (90.0-108.0)	0.054
Neck (cm)	40.0 (36.0-45.0)	42.0 (34.0-45.0)	41.0 (35.0-43.0)	0.14
Glycemia (mg/dL)	90.7 (89-101.0)	93.0 (72.0-107.0)	93 (79.0-101.5)	0.45
% Diabetes	20.0	29.6	17.2	0.33
HLD (mg/dL)	42.2 (34.0-48.0)	41 (39.2-44.0)	35 (19.0-44.5)	0.16
TGL (mg/dL)	83.5 (60.0-132.5)	106.8 (46.0-1140.0)	112.8 (45.0-160.0)	0.24
Hematocrit (%)	39.0 (37.0-41.2)	41 (39.2-44.0)	43.0 (41.0-45.0)	< 0.01
Hemoglobin (g/dL)	13.0 (12.5-13.5)	14.0 (13.0-14.8)	13.9 (13.9-15.2)	< 0.001
SAP	138.5 (124.5-140.0)	135.0 (120.0-143.8)	135.0 (122.0-147.0)	0.72
% SAP > 130	70	54.6	61.4	0.5
DAP	85.7 (72.0-94.0)	83.0 (70.0-83.0)	80 (68.0-84.0)	< 0.05
% DAP > 85	80.0	62.5	45.6	< 0.05
% AHT	90.0	89.5	80.7	0.6

(SAP: systolic arterial pressure, DAP: diastolic arterial pressure)
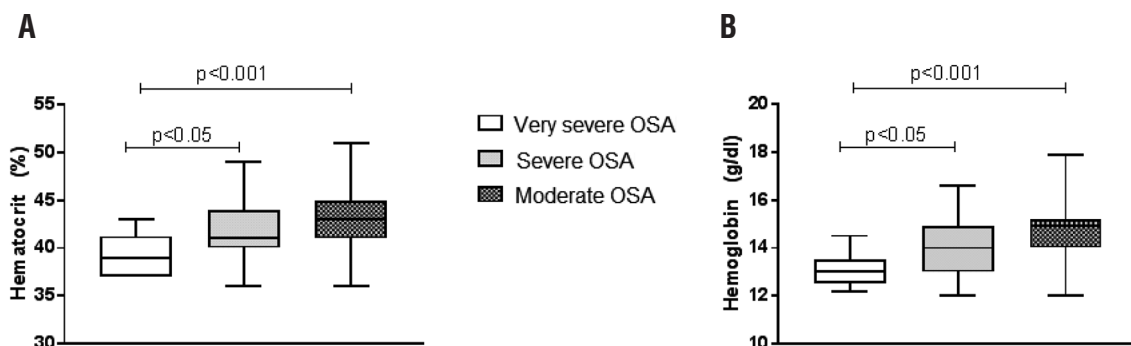
Figure 2. Laboratory parameters of patients with OSA grouped according to the severity. A) Hematocrit and B) Hemoglobin.

Table 1 shows a proportional increase in the amount of patients with AHT in terms of severity by the AHI. However, the AMAP results showed a statistically significant increase only in the DAP (diastolic arterial pressure) of patients with very severe OSA, in comparison with the severe and moderate OSA groups (94 ± 7.7 vs. 87.9 ± 8.7 and 84.4 ± 8.2; $p < 0.05$ and $p < 0.01$ respectively), **Figure 3A and B**.
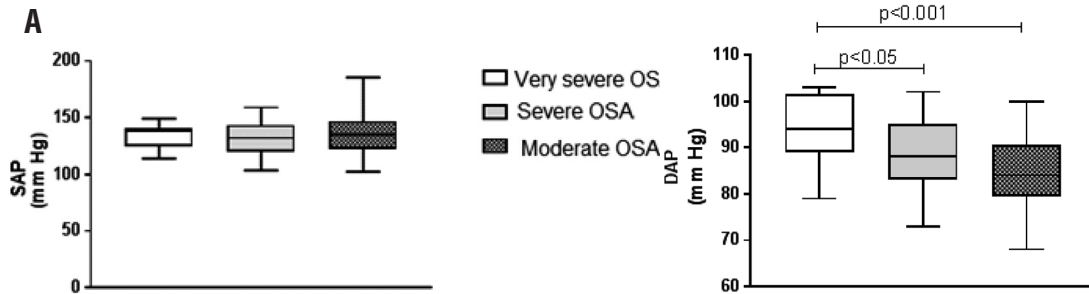
Figure 3. systolic arterial pressure (A) and diastolic arterial pressure (B) grouped according to OSA severity.

Within the vsOSA group, despite the severity per AHI (mean of $69.0 \pm 63.5\text{-}75.5$ events/hour), no significant differences were observed in the Somnolence Scale (ESS) or the SBQ Questionnaire (**Table 2**).

TABLE 2. Recording of the variables obtained in the respiratory polygraphs (TRT: total recording time)

	Very severe OSA	Severe OSA	Moderate OSA	p
N	10	48	57	
TRT (minutes)	421 (342.5-465.5)	403 (334.5-460.0)	393 (357.0-457.3)	0.9
ESS	7 (2-10)	7 (5-10)	8 (5-11)	0.5
% w/ESS > 10	20	25	28	0.8
% w/High Berlin	100	100	100	0.2
SBQ	3 (2.0-4.25)	4 (3.0-4.7)	4 (3-6)	0.4
% SBQ ≥ 5	20.0	25.0	31.0	0.6
AHI (ev/hour)	69.0 (63.5-75.5)	36 (34.0-47.0)	20.1 (17.1-23.1)	< 0.001
ODI (ev/hour)	68.0 (63.5-75.5)	39.5 (31.7-47.0)	20.0 (16.9-23.4)	< 0.001
T90%	41.5 (19.5-63.5)	24.5 (13.5-53.2)	13.0 (8.0-28.2)	< 0.001

(TRT) = Total Recording Time in the respiratory polygraphy. ESS Epworth Subjective Sleepiness Scale.
SBQ: number of components of the STOP-BANG Questionnaire

Patients with vsOSA showed a significant increase in the desaturation index (ODI) compared to the severe and moderate OSA groups (69.5 ± 7.8 vs. 39.1 ± 9.8 and 20.4 ± 5.2; $p < 0.05$ and $p < 0.001$) respectively. (**Figure 4A**). Further; the percentage of time with a saturation less than 90% also showed a significant difference in patients with very severe OSA compared to moderate OSA (44.3 ± 24.2 vs. 21.3 ± 20.7; $p < 0.01$) (**Figure 4B**).
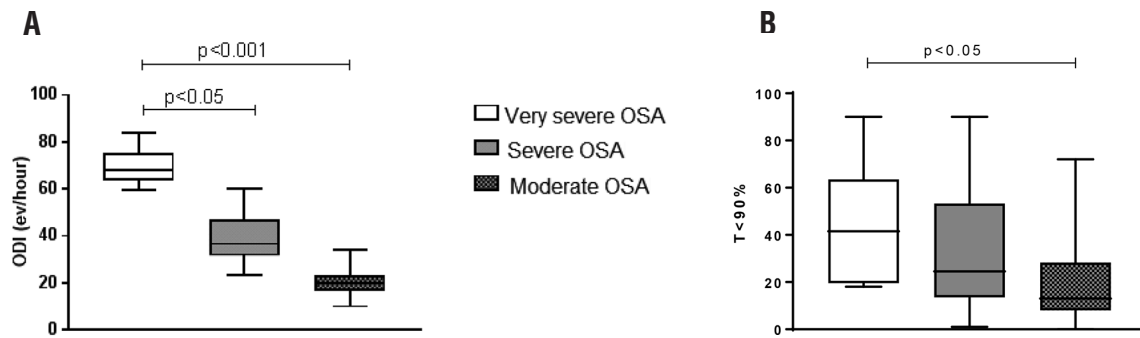
Figure 4. Oximetry indexes; in desaturations per hour (ODI) threshold 3% and time below 90% (T < 90%) grouped according to severity of OSA.

Discussion

This sample consisted of 115 patients with OSA, AHI ≥ 15 and cardiovascular risk, 10% of which met the criteria established by us to be categorized as vsOSA.

The severity of OSA has been traditionally evaluated according to the AHI. However, this indicator used separately seems to reflect the severity of the OSA in an insufficient manner, thus we recommend that it is complemented with the assessment of severity modifying factors (degree of hypoxemia, sleep fragmentation, duration and distribution of the events, symptoms, age, etc)[20].

Recently, an association has been described between the severity of the OSA and the increase of reactive oxygen species[21]. Though it hasn't been the purpose of this study, those findings could be related to the increase in patients' hypoxemia according to the increase in the severity. The results of this study have shown a significant increase evidencing a higher ODI and T< 90.

Previous studies have shown that patients with very severe OSA present a higher degree of nocturnal hypoxemia expressed by an increase in indicators such as time with < 90% saturation (T < 90%) and more comorbidities, as for example, arterial hypertension[11, 12]. Our findings, in agreement with those authors, showed a significant increase in T < 90%, in the ODI and in the proportion of patients with DAP > 85 within the group of patients with very severe OSA in comparison with patients with severe and moderate OSA.

Preis et al, in a study derived from the Framinghan study database, found a relationship between anthropometric parameters and the probability to develop cardiovascular events associated with OSA. But, in hypertensive patients, we didn't find any differences in variables such as waist and neck circumference, the degree of obesity evaluated with the BMI or in TGL or HDL blood levels[22].

One of the comorbidities frequently associated with the OSA is diabetes[23]. A deregulation of glucose metabolism in patients with OSA has been suggested, though it isn't clear yet if this alteration is related to severity. Our findings didn't show discrepancies in terms of glycemia among the different severity groups.

Also Nieto et al have shown that the incidence of arterial hypertension in patients with OSA becomes higher as severity increases[24]. In line with such report, our findings showed a significant increase in patients with DAP > 85 mmHg; but no statistical power was achieved for the percentage of patients diagnosed with AHT.

Nguyen et al evaluated in a cohort the hematocrit levels in groups of patients with OSA of different severity levels; however no statistically significant differences were observed[25]. Surprisingly, in this study, significant differences were found regarding hematocrit and hemoglobin levels with an inverse correlation, though within the normality range and with low clinical relevance.

In accordance with the findings of our sample, patients with vsOSA, categorized by an AHI ≥60, showed greater deterioration in the oxygenation indicators measured during sleep, compared to patients with mOSA and sOSA according to conventional criteria. In this limited sample, we didn't identify significant differences in the other evaluated parameters, such as weight, neck circumference or metabolic

indicators, but we did find a higher incidence of diastolic AHT. Rey de Castro et al have described the need to identify prognosis variables for the very severe manifestations of sleep apneas[12].

Surprisingly, we haven't found in our series any differences in the clinical presentation, the degree of subjective somnolence or the results of prediction questionnaires between vsOSA and moderate to severe manifestations of the disease, thus suggesting the difficulty to identify them before the sleep study.

Limitations

The main limitation of this study was related to the poor number of cases identified as vsOSA; for that reason, confidence intervals were wide. However, the population included represents real life and the group of patients generally referred to specialized heart centers. The clinical characteristics evaluated in patients have been only those representing the work system of our Arterial Hypertension Unit. We propose the future study of inflammatory variables in order to understand the physiological mechanisms related to this extreme group of patients with sleep apneas.

Another limitation is placed by confusion variables related to the OSA and the fact that they were evaluated by simplified methods. The diagnostic capacity of the respiratory polygraphs we used is limited, though they all included at least the 3 basic signals on which manual reading and final interpretation of the sleep study were based. The home RP could establish differences between our results and the results of other studies using polysomnography (PSG) at the sleep lab[11-12]. In comparison with the conventional PSG, the RP has 10-15% underestimation rate for the AHI, a limitation that is inherent to the absence of neurophysiological signals[18-19]. The indexes that were used (AHI and ODI) differ from those of the PSG in that they are the result of the quotient between the events and the total recording time, though they represent a diagnosis standard in our area.[10]

Finally, our analysis included a little sample of non-obese patients, thus limiting our interpretation. Also, we only considered one evaluation with no follow-up. Longitudinal studies will be necessary to know the clinical and predictive value of these extreme manifestations of the disease.

Conclusion

In our very limited sample of patients with vsOSA, we identified a higher incidence of diastolic AHT and greater deterioration in the oximetry variables, but found no differences in the clinical parameters and other metabolic data under evaluation.

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