UNIVERSITÀ
POLITECNICA
DELLE MARCHE

FACOLTÀ DI MEDICINA E CHIRURGIA

Dipartimento di Scienze Cliniche e Molecolari

Ph.D. program Human Health

Cycle XXXIV

Predictors of moderate and severe obstructive sleep apnea and association of nocturnal oximetry parameters with cardiovascular organ damage

Tutor:

Prof. Riccardo Sarzani

Ph.D. Candidate:

Federico Giulietti

2018-2021

TABLE OF CONTENTS

ABSTRACT

Background: Obstructive sleep apnea (OSA) affects nearly one billion people worldwide, with increasing prevalence. Most of the OSA-related morbidity and mortality is linked to an increased risk of developing and/or progressing cardiovascular disease (CVD). The marker most often used to define both the disease severity and the risk for organ damage is the apnea-hypopnea-index (AHI). The search for predictors of OSA is in continuous progress. The aim of this study was to evaluate the predictors of moderate and severe disease in a large unselected sample of patients affected by OSA and investigate the association of nocturnal oximetry parameters with CV organ damage.

Methods: Observational cross-sectional study on 618 consecutive outpatients referred to our unit at INRCA-IRCCS (Ancona, Italy), between October 2018 and January 2020, diagnosed with OSA after performing home cardiorespiratory polygraphic recording. In addition to the polygraphic parameters, several other clinical parameters have also been collected: anthropometric data, symptoms and signs, comorbidities, laboratory parameters, blood pressure (BP) parameters and drug therapy, and their associations with OSA have been analyzed. The main oximetry parameters were grouped using a factor analysis into a single parameter (Oxy-score) and its association with CV organ damage has been investigated.

Results: Mean age was 61.0±13.6 years with male prevalence (72.5%). Prevalence of overweight/obesity was 90.3%. Arterial hypertension and dyslipidemia were the most prevalent CV risk factors (77.7% and 78.7%, respectively), while hypertensive heart disease and peripheral arterial disease were the most prevalent CVD (69.9% and 63.8%, respectively). The prevalence of oAHI≥15 and oAHI≥30 was 71.7% and 35.8%, respectively. Macroglossia (OR=4.2, p<0.001), neck circumference >43cm (OR=3.0, p=0.008), witnessed breathing pauses (OR=2.3, p=0.019), excessive daytime sleepiness

(OR=5.4, p=0.049), and arterial hypertension (OR=3.0, p=0.003) were independent predictors of moderate OSA. Neck circumference >43cm (OR=4.5, p<0.001), nocturia (OR=3.5, p=0.013) and a non-dipper/reverse dipper BP pattern (OR=6.3, p=0.003) were independent predictors of severe OSA. Oxy-score was associated with the presence of CVD, especially hypertensive heart disease, even after adjusting for covariates (OR=0.45, p=0.044), regardless oAHI.

Conclusion: This study confirms the role of several clinical features, such as neck circumference, nocturia, excessive daytime sleepiness, arterial hypertension and a non-dipper/reverse dipper BP pattern as predictors of moderate and severe OSA. It also highlights the association between oximetry parameters and CVD, especially hypertensive heart disease, regardless of oAHI, thus providing interesting insights for future prospective studies aimed at further defining the predictors of OSA and the role of oximetry parameters in determining both the disease severity and the risk of OSA-related CVD.

KEYWORDS

Obstructive sleep apnea; home cardiorespiratory polygraphy; predictor; oximetry parameters; organ damage; cardiovascular disease; hypertension; dipping; macroglossia; neck size; nocturia; excessive daytime sleepiness.

INTRODUCTION

Obstructive sleep apnea (OSA) is a growing public health concern, affecting nearly one billion people worldwide [1]. The prevalence of OSA has increased in recent decades, parallel to the steady increase in the prevalence of overweight and obesity [2,3], mainly affecting middle-aged and older men [4]. However, it is important to note that OSA is still often underdiagnosed, with estimates of around thirty million missed diagnosis in Europe alone [1]. The recurrent partial or complete upper airway collapse during sleep, followed by intermittent hypoxia and recurrent arousals, leading to sleep fragmentation, poor sleep quality and therefore non-restorative sleep and excessive daytime sleepiness, are the most historically traditional traits of the disease [5,6], associated with worst quality of life, cognitive dysfunction and a higher risk of road accidents [7,8]. However, most of the morbidity and mortality risk associated with OSA is closely linked to an increased risk of developing and/or progressing cardiovascular diseases [9]. Indeed, OSA has been associated with higher risk of arterial hypertension and worse blood pressure control, impaired lipid and glucose metabolism, coronary artery disease, arrhythmias, heart failure and stroke [10–12]. The OSA severity is traditionally defined by the apnea-hypopnea index (AHI), but its value as a marker able to predict cardiovascular disease is limited. Therefore, alternative classification methods, better capable to capture and stratify the cardiovascular risk of OSA patients, such as the hypoxic burden, other polysomnographic traits, and phenotypes based on clinical symptoms, are emerging [13]. The aim of the present study was to evaluate the predictors of moderate and severe obstructive sleep apnea in a large unselected sample of patients affected by OSA and investigate the association of nocturnal oximetry parameters with cardiovascular organ damage.

METHODS

Study design and population

This was an observational cross-sectional study on 618 consecutive outpatients referred to our Respiratory Care Medicine and European Society of Hypertension (ESH) Excellence Centre at the Internal Medicine and Geriatrics Unit of the Italian National Institute of Health and Science on Ageing (INRCA IRCCS, Ancona, Italy), between October 2018 and January 2020, diagnosed with obstructive sleep apnea. Most patients were referred to our centre by general practitioners, while only a minor part by other specialists, for a suspicion of obstructive sleep apnea. Therefore, our sample reflects well a community-dwelling population affected by obstructive sleep apnea. We applied the following inclusion criteria: patients aged ≥ 18 years diagnosed with obstructive sleep apnea, defined as the presence of an obstructive apnea-hypopnea index (oAHI) of at least five events per hour of valid recording time at a cardiorespiratory polygraphic recording, according to the 2011 Recommendations for the Diagnosis and Treatment of the Sleep Breathing Disorders of the Italian Association of Hospital Pulmonologists (Associazione Italiana Pneumologi Ospedalieri, AIPO) [14]. We applied the following exclusion criteria: a valid recording time of less than four hours, inadequate quality of the cardiorespiratory signals not allowing a proper interpretation of the polygraphic recording of at least four hours, a manteinance of the supine position for less than 10% of the valid recording time [14]. All participants gave their informed written consent and clinical investigations have been conducted according to the principles expressed in the Declaration of Helsinki. This study was approved by the local institutional ethics committee (Comitato Etico INRCA).

Clinical parameters

Before placing the cardiorespiratory monitoring, each patient underwent a medical examination, in which the following clinical parameters were taken into account: medical history, where all the comorbidities have been recalled, daytime and nighttime symptoms and signs, in particular objective daytime sleepiness, that was evaluated using the Epworth Sleepiness Scale (ESS) [15] and defined as a score at ESS > 10, habitual snoring, witnessed breathing pauses, choking, morning dry mouth and morning headache, nocturia (defined as two or more urinations per night), night sweats, attention/concentration/memory impairment, the pre-test risk of OSA assessed using the Berlin questionnaire [16], anthropometric measurements, office blood pressure measurements, cardiovascular drug therapy. Among the anthropometric measurements, body mass index (BMI) was defined as the body mass divided by the square of the body height and was expressed in units of kg/m^2; patients with BMI $\geq$ 25 kg/m^2 were defined overweight/obese (OW/OB). Waist circumference was measured to the nearest 0.1 cm, at the midpoint between the lowest rib and the iliac crest with patients unclothed to the waist. Neck circumference was measured to the nearest 0.1 cm, at the middle of the neck between the mid-cervical spine and superior line of the cricothyroid membrane in a standing position. Macroglossia was defined as a resting tongue protruding beyond the teeth or alveolar ridge. The Mallampati score was used as an objective measure of soft tissue crowding of the oropharynx [17]. Smoking status was ascertained during the visit and smoking habit was defined as current smoking or previous smoking of at least 100 cigarettes in a lifetime [18]. Arterial hypertension, dyslipidemia and impaired glucose metabolism/type 2 diabetes mellitus, as well as the other several comorbidities taken into account, were defined on the basis of documented medical history and/or the use of appropriate drug treatment. Furthermore, ambulatory blood pressure

parameters and laboratory parameters were also taken into account, when available and if performed within three months and within a year prior to the clinical visit, respectively. The following fasting laboratory parameters were taken into account: glycaemia, total cholesterol, high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc), that was calculated using a modified Friedewald method proposed by Martin et al [19], triglycerides, non-HDLc (calculated by subtracting HDLc from total cholesterol), creatinine, estimated glomerular filtration rate (eGFR) using the CKD-EPI creatinine equation, thyroid-stimulating hormone (TSH). Both blood pressure and LDLc control were defined according to the latest published guidelines of the European Society of Cardiology, on the basis of the individual cardiovascular risk [20,21].

Polygraphic parameters

Patients were evaluated using the following type III portable devices for cardiorespiratory monitoring, or home sleep apnea testing (HSAT): Somnocheck 2, Weinmann, Hamburg (Germany) or Somtè, Compumedics, Singen (Germany). The device was placed after the clinical visit by the same trained physician, and a sleep diary was given to the patient at the end of the visit, where he had to record several important informations, such as the time of falling asleep and the time of awakening in the morning, the presumed duration of the sleep period, any nocturnal awakenings and their duration, the intake of substances or drugs that could affect sleep. On the next day, the patient had to bring the device back to the office and the recording was evaluated using dedicated softwares. After descarding from the total bed time the portions of time in which the patient was presumably awake, on the basis of both the information obtained from the sleep diary and from the polygraphic signals, the valid recording time was obtained and the manual scoring of the respiratory events during sleep

could be performed, by the same trained physician in order to avoid interobserver bias, according to the 2011 Recommendations for the Diagnosis and Treatment of the Sleep Breathing Disorders of the Italian Association of Hospital Pulmonologists (Associazione Italiana Pneumologi Ospedalieri, AIPO) [14]. The poligraphic parameters taken into account were the following: apnea-hypopnea index (AHI), that was further subdivided into its obstructive (plus mixed) component (oAHI) and its central component (cAHI); oxygen desaturation index (ODI 4%), mean peripheral oxygen saturation (SpO2) and minimum (nadir) SpO2; time spent with SpO2 below 90% (T90%), mean of desaturations and severity of desaturations, defined on the basis of the mean of desaturations ("mild" if above 90%, "moderate" if between 85 and 90%, and "severe" if below 85%), time (%) spent on supine position and presence of positional OSA (pOSA) defined as a ratio between supine AHI and non-supine AHI ≥ 3. On the basis of the oAHI, the degree of OSA severity was defined as "mild" if oAHI ≥ 5 and < 15, "moderate" if oAHI ≥ 15 and < 30, or "severe" if oAHI ≥ 30. The presence of a respiratory pattern characterized by at least three cycles of hypoventilation-hyperventilation with a typical waxing-waning pattern of tidal volume, lasting at least ten consecutive minutes and a cAHI ≥ 5 were used to define the presence of Cheyne-Stokes breathing (CSB-CSA). A T90% ≥ 30% of the valid recording time was used to define the presence of nocturnal hypoxemia [14].

Blood pressure parameters, cardiovascular drug therapy and cardiovascular organ damage

During the clinical visit, three consecutive oscillometric automatic blood pressure (BP) measurements have been performed on both arms, using a validated device (Watch BP Office, Microlife, Widnau, Switzerland). Correct cuff sizes (range 22-32 cm or 32-42 cm) were selected according to arm circumference and BP measurements were performed after

at least 5 minutes of rest in the sitting position. The patient's arm was kept at the heart level during the measurement. The arm with higher reading was taken into account for the analysis. As regards to the ambulatory BP monitoring (ABPM), we took into account the minimum quality criteria for a satisfactory recording based on recommendations by Omboni et al [22]. For each patient who underwent ABPM, 24-hour BP, daytime BP (defined as the BP values from 06:00 to 22:00 hour), night-time BP (defined as the BP values from 22:00 to 06:00 hour), 24-hour, daytime and nighttime pulse pressures (obtained by subtracting the diastolic BP values from the systolic BP values) were taken into account. The definitions of "day" and "night" periods were based on the most common patients sleeping behaviors. Patients with mean 24-hour BP <130/80 mmHg, mean daytime BP <135/85 mmHg, and mean night-time BP <120/70 mmHg were defined as controlled [20]. We defined "dippers" those patients with a mean systolic BP reduction equal to or greater than 10% from day to night, "non dippers" those patients with a mean systolic BP reduction of less than 10% from day to night, and "reverse dippers" those patients with nighttime mean systolic BP higher than mean daytime systolic BP [20].

Cardiovascular drug therapy was also taken into account, in particular antihypertensive drugs, such as angiotensin-converting-enzyme inhibitors (ACE-I) or angiotensin II-type 1 receptor antagonists (ARB), diuretics, beta-blockers and dihydropyridine calcium channel blockers (CCB), statin therapy, antiplatelet and anticoagulant therapy. Regarding antihypertensive drug therapy, the treatment intensity score (TIS) was used to compare different drug associations. As previously reported [23], the recorded daily dose taken by patients was divided by the maximum recommended daily dose to obtain a proportional dose (intensity) for that medication. The maximum recommended daily doses established by the Italian National Drug Agency (AIFA) were used for these calculations. Dual-class drugs

were separated into their components and intensity was calculated separately for each compound. The sum of all the different values was recorded as the TIS.

The following parameters of cardiovascular organ damage were taken into account, when available from patients' hystory: hypertensive heart disease at echocardiography, namely the presence of left ventricular hypertrophy according to the 2018 ESC-ESH Guidelines on arterial hypertension [20], known peripheral arterial disease (PAD) defined as the presence of atherosclerotic plaques at carotid and/or lower limb arteries detected at doppler ultrasound, known chronic kidney disease (CKD) (defined as an eGFR < 60 ml/min/1.73 m^2 in at least two consecutive measurements performed at least three months apart), office and ambulatory pulse pressure (PP) ≥ 60 mmHg and ≥ 55 mmHg, respectively, as surrogate markers of vascular disease [24], and prior cardiovascular events, such as hystory of coronary artery disease (CAD) and/or transient ischemic attack(TIA)/stroke.

Statistical Analysis

Data were analyzed with the Statistical Package for Social Science version 21 (SPSS Inc. Chicago, Illinois, USA). A p-value less than 0.05 was defined as statistically significant. Continuous variables were checked for normality. Normal continuous variables were expressed as mean ± standard deviation (SD). Skewed variables were expressed as median and interquartile range. Categorical variables were expressed as percentages. The $\chi 2$ test was used to analyze the differences between categorical variables. The unpaired t test and Mann-Whitney test were used to compare quantitative variables. Logistic regression analyses were used to create adjusted models. Variables with significant associations with oAHI≥15 and oAHI≥30 identified upon univariate analyses were tested within stepwise logistic regression models (entry value = 0.05 and removal value = 0.10) to evaluate the predictors of moderate

and severe OSA. In order to reduce the main oximetry variables in a single factor (Oxy-score), a factor analysis has been performed. The Kaiser-Meyer-Olkin method (minimum required specified adequacy level > 0.6) and Bartlett test of sphericity were performed to estimate the adequacy of the data for our model. Eigenvalues greater than one and a scree plot were used to determine the number of retained factors. We used Principal Axis Factoring as extraction method. Receiver operating characteristic (ROC) analysis was used to determine the predictive ability of oAHI and Oxy-score for hypertensive heart disease. Then, a comparison of the two ROC curves has been performed to determine the presence of a difference between the predictive ability of the two parameters.

RESULTS

General characteristics of the study population

In the present study, 618 patients have been evaluated. General characteristics of the entire study population, and according to age and sex, are described in Table 1. The age of recruited patients ranged from 18 to 92 years and male sex was prevalent (72.5%). Over 90% of patients were overweight and over half of the patients were obese, especially women (61.2% vs 51.8%, p=0.036), and with central adiposity. Almost all patients had a Mallampati class III or IV, and over 80% of patients had macroglossia at body examination, especially men (84.2% vs 73.0%, p=0.004). Nearly 90% of patients resulted at high risk at Berlin questionnaire and women were found to be more sleepy than men at the Epworth Sleepiness Scale (19.2% vs 12.6%, p=0.040 for excessive daytime sleepiness between women and men). A sedentary lifestyle was highly prevalent (79.6%), as well as the smoking habit, especially in men (67.3% vs 49.0%, p<0.001). The prevalence of chronic insomnia was higher in women (35.7% vs 18.3%, p<0.001) as well as the prevalence of anxiety and/or depression (33.6% vs 14.9%, p<0.001). Arterial hypertension and dyslipidemia were the most prevalent cardiovascular risk factors among the entire study sample (77.7% and 78.7%, respectively), while hypertensive heart disease and PAD were the most prevalent cardiovascular diseases (69.9% and 63.8%, respectively). Older patients had a higher prevalence of all comorbidities, as expected, except chronic insomnia, anxiety and/or depression and gastroesophageal reflux disease. Regarding nighttime and daytime symptoms and signs, men had higher prevalence of witnessed breathing pauses than women (77.7% vs 60.7%, p<0.001), while women had higher prevalence of both subjective excessive daytime sleepiness (57.9% vs 45.6%, p=0.014) and morning headaches (37.1% vs 16.9%, p<0.001). Nocturia was more prevalent in older patients (77.0% vs 45.2%, p<0.001), as expected,

however nearly half of the younger patients reported it, while no difference was found between man and women. Both office and ambulatory blood pressure control rates, especially during nighttime, were low in this study (12.5%, 29.9% and 20.3%, respectively), as well as the low-density-lipoprotein cholesterol control rate (8.6%), according to the individual cardiovascular risk, with no difference according to age and sex. Regarding laboratory parameters and cardiovascular drug therapy, older patients had lower values of eGFR (74.1±21.7 vs 86.7±17.5 ml/min/1.73m^2, p<0.001), as expected, and also lower blood lipids values, except HDLc, and higher prevalence of both statin therapy (62.2% vs 29.0%, p<0.001) and antihypertensive therapy (84.5% vs 61.6%, p<0.001) than younger patients, as well as higher prevalence of all the other drug classes taken into account.

Polygraphic characteristics of the study population

Polygraphic characteristics of the entire study population and according to age, sex and body mass index are described in Table 2. Men had higher prevalence of both obstructive (28.9±19.7 vs 24.0±15.9, p=0.002) and central sleep events (2.0±4.4 vs 0.8±1.7, p<0.001) than women, as well as higher prevalence of desaturations during sleep (35.8±23.1 vs 28.9±19.0, p<0.001), with a trend of worse oxygen parameters. Older patients had significant worse oxygen parameters than younger patients (all p<0.05), as well as obese patients had significant worse oxygen parameters than non-obese patients (all p<0.001), as expected. On the other hand, non-obese patients had higher prevalence of positional OSA than obese patients (21.7% vs 9.5%, p<0.001).

Ambulatory blood pressure parameters according to OSA severity

In 187 patients with an available valid ambulatory BP recording, the associations bewteen ABPM parameters and the degree of OSA have been evaluated and described in Table 3. There were no significant differences in ABPM parameters between patients with oAHI < 15 and patients with oAHI ≥ 15. On the other hand, patients with severe OSA had a significantly higher nighttime PP than patients with milder OSA (55.8±12.5 mmHg vs 51.6±12.1 mmHg, p=0.019) and, above all, a higher prevalence of non-dipper/reverse-dipper pattern than patients with milder OSA (90.9% vs 65.8%, p<0.001).

Predictors of obstructive sleep apnea

The predictors of OSA have been investigated starting from univariate analyses, as described in Table 4. While both male sex and older age were found to predict moderate OSA (OR=1.6, p=0.018 and OR=1.4, p=0.049, respectively), only male sex was found to predict severe OSA (OR=1.5, p=0.043). The strongest predictors of moderate OSA were found to be a neck circumference > 43 cm (OR=7.6, p<0.001), a Mallampati class III-IV (OR=5.6, p<0.001) and macroglossia (OR=5.1, p<0.001), among the body examination parameters; a high risk at Berlin questionnaire (OR=3.7, p<0.001); having arterial hypertension (OR=2.9, p<0.001) and PAD (OR=2.5, p<0.001), among the comorbidities; witnessed breathing pauses (OR=2.4, p<0.001), both objective excessive daytime sleepiness, evaluated with the ESS, (OR=3.4, p<0.001) and subjective excessive daytime sleepiness, reported by patients during the clinical visit (OR=2.2, p=0.001), and nocturia (OR=2.7, p<0.001) among the nighttime and daytime symptoms and signs. The strongest predictors of severe OSA, were found to be a Mallampati class III-IV (OR=14.6, p<0.001), being overweight/obese (OR=5.6, p<0.001), macroglossia (OR=5.5, p<0.001) and a neck circumference > 43 cm (OR=5.0, p<0.001)

among the body examination parameters; a high risk at Berlin questionnaire (OR=3.2, p<0.001); having had a TIA/stroke (OR=2.6, p=0.008) and having an impaired glucose metabolism (OR=2.5, p<0.001), among the comorbidities; nocturia (OR=3.4, p<0.001) and both subjective excessive daytime sleepiness, reported by patients during the clinical visit (OR=2.7, p<0.001) and objective excessive daytime sleepiness, evaluated with the ESS, (OR=2.2, p=0.001), among the nighttime and daytime symptoms and signs; having a non-dipper/reverse dipper pattern (OR=5.2, p<0.001). After performing forward stepwise logistic regression analyses (Table 5), macroglossia (OR=4.2, p<0.001) and a neck circumference > 43 cm (OR=3.0, p=0.008) were found to be the strongest predictors of moderate OSA, among the body examination parameters; witnessed breathing pauses (OR=2.3, p=0.019) and objective excessive daytime sleepiness, evaluated with the ESS, (OR=5.4, p=0.049), among the nighttime and daytime symptoms and signs; arterial hypertension (OR=3.0, p=0.003) among the comorbidities. Regarding the predictors of severe OSA, a neck circumference > 43 (OR=4.5, p<0.001) was found to be the only strong independent predictor among the body examination parameters and nocturia (OR=3.5, p=0.013) was found to be the strongest independent predictor among the nighttime and daytime symptoms and signs. Furthermore, having a non-dipper/reverse dipper pattern (OR=6.3, p=0.003) was also found to be a strong independent predictor of severe OSA (Table 5).

Associations between polygraphic parameters and cardiovascular organ damage/ cardiovascular events

The associations between polygraphic parameters and both the markers of cardiovascular organ damage and cardiovascular events taken into account in the present study have been investigated and described in Tables 6a and 6b, respectively. Patients with hypertensive heart

disease had a higher number of obstructive events than patients without hypertensive heart disease (31.4±18.7 vs 24.4±18.1, p=0.001), coupled with significantly worse oximetry parameters: higher ODI (39.5±22.1 vs 29.4±21.5, p<0.001), lower mean SpO2 [93 (91-94) vs 94 (93-96), p<0.001)], lower nadir SpO2 (74.7±9.2 vs 79.5±8.0, p<0.001), higher T90 [10.5 (3.1-27.0) vs 1.9 (0.1-8.7), p<0.001], and lower mean of desaturations [89 (85-90) vs 90 (89-92), p<0.001]. Same significant associations were found with PAD. Regarding the association with CKD, only weaker associations with lower nadir SpO2 (74.0±9.1 vs 76.4±9.1, p=0.049) and higher T90 [12.5 (3.5-26.9) vs 7.0 (1.4-21.0), p=0.025] have been found. Patients with a 24-PP≥55 mmHg had a higher number of obstructive events than patients with a 24-PP<55 mmHg (34.9±20.5 vs 29.3±17.9, p=0.048), while this associations has not been found for patients with office PP≥60 mmHg, that had however worse oximetry parameters than patients with office PP<60 mmHg: higher ODI (40.9±22.9 vs 33.9±21.0, p=0.008), lower mean SpO2 [93 (91-94) vs 94 (92-95), p=0.002], lower nadir SpO2 (74.2±9.4 vs 77.0±8.8, p=0.011), higher T90 [12 (3-25) vs 7 (1-20), p=0.017].

Regarding the associations with cardiovascular events (Table 6b), patients with hystory of CAD had worse oximetry parameters than patients without hystory of CAD: lower mean SpO2 [93 (90-94) vs 94 (92-95), p=0.001], lower nadir SpO2 (72.9±9.8 vs 76.8±9.0, p=0.001), higher T90 [13 (4-37) vs 6 (1-18), p=0.001] and lower mean of desaturations [89 (85-90) vs 90 (86-91), p=0.001]. Regarding patients with hystory of TIA/Stroke, the only significant association found was with a higher ODI (45.1±17.5 vs 35.6±22.6, p=0.019), and a trend toward both higher number of obstructive events and worse remaining oximetry parameters, but without reaching the statistical significance.

Factor analysis

A factor analysis has been performed, in order to group the main oximetry variables taken into account (ODI, mean SpO2, nadir SpO2, mean of desaturations, and T90) in a single factor. Testing of assumptions revealed adequacy of the dataset to conduct a factor analysis. The Kaiser-Meyer-Olkin measure of Sampling Adequacy (0.85) was greater than the specified level of 0.60 and Bartlett Test of Sphericity was significant (2457.02, $p<0.001$). After using Principal Axis Factoring as extraction method and a scree plot to determine the number of retained factors, only one factor was extracted with Eigenvalues greater than one, that accounted for 75.8% of variance. This factor has been termed as "Oxy-score" (0±1, range from -5.0 to 1.5). Oxy-score was directly correlated with nadir SpO2 (R=0.787), mean SpO2 (R=0.878) and mean of desaturations (rho=0.927) (all $p<0.001$), and it was inversely correlated with ODI (R=-0.722) and T90 (rho=-0.859) (all $p <0.001$). In summary, the lower the Oxy-score value, the worse the patient's oxygenation.

Association between Oxy-score and cardiovascular organ damage/cardiovascular events

After extracting the Oxy-score using factor analysis, the associations between Oxy-score and both markers of cardiovascular organ damage and cardiovascular events have been evaluated (Table 7). At univariate analysis, Oxy-score was found to be associated with hypertensive heart disease (OR=0.40, $p<0.001$), PAD (OR=0.54, $p<0.001$), office PP≥60 mmHg (OR=0.77, p=0.039) and 24-h PP≥55 mmHg (OR=0.72, p=0.029), among markers of cardiovascular organ damage. Regarding cardiovascular events, Oxy-score was found to be associated with CAD (OR=0.71, p=0.002). After adjusting for covariates (age, sex and oAHI), Oxy-score was found to remain independently associated with hypertensive heart

disease (OR=0.44, p<0.001) and PAD (OR=0.64, p=0.007), as well as with CAD (OR=0.57, p=0.001).

Oxy-score and hypertensive heart disease

In order to determine the predictive ability of both oAHI and Oxy-score for hypertensive heart disease, receiver operating characteristic (ROC) analysis has been performed. The AUC for oAHI was 0.63 (95% CI 0.59-0.68) and the AUC for Oxy-score was 0.70 (95% CI 0.65-0.74). Then, a comparison of the two ROC curves has been performed, finding a significant difference between the predictive ability of the two parameters (p=0.005), as described in Figure 1. Logistic regression analyses have also been performed to confirm the independent association between Oxy-score and hypertensive heart disease, in patients who had performed ABPM (Table 8). In model 1, oAHI was found to be a significant independent predictor of hypertensive heart disease (OR=1.03, p=0.039), after age (OR=1.10, p<0.001) and 24-hour BP control (OR=0.18, p<0.001), respectively. In model 2, the Oxy-score input (OR=0.45, p=0.044) resulted in the oAHI output (p=0.759) from the model, confirming the independent predictive power of Oxy-score over oAHI for hypertensive heart disease.

DISCUSSION

In the present study involving 618 consecutive outpatients affected by OSA, both the predictors of moderate and severe OSA and the association between oximetry parameters and cardiovascular organ damage have been extensively investigated. Several independent predictors of moderate OSA (defined by an oAHI ≥ 15/hour) have been found in different domains, such as neck circumference, especially a neck circumference > 43 cm, and macroglossia, among the parameters evaluated at body examination, or objective daytime sleepiness, evaluated with Epworth Sleepiness Scale, among the symptoms and signs, or arterial hypertension among the comorbidities. On the other hand, with regard to the predictors of severe OSA (defined by an oAHI ≥ 30/hour), while a neck circumference > 43 cm confirmed its independent predictive role, nocturia as well as the presence of a non dipper/reverse dipper blood pressure pattern were found to be the strongest independent predictors among symptoms and signs. Moreover, an association between oximetry parameters and cardiovascular organ damage, especially hypertensive heart disease, has been found regardless OSA severity (traditionally defined by oAHI), confirming the independent link between OSA-related hypoxia and both arterial hypertension and hypertension-mediated organ damage.

Among the risk factors for OSA, male sex, older age, and obesity are usually regarded as the most classic and best known [25]. Although the risk of OSA correlates with BMI, and obesity remains the one major modifiable risk factor for OSA [26], it is important to note that also normal weight or even underweight patients can suffer from OSA, especially in the presence of craniofacial anatomic abnormalities that can narrow the upper airway. Moreover, it is important to note that beyond BMI, an even stronger correlation exists between OSA and increased neck size [25]. Neck sizes greater than 17 and 16 inches (43

cm and 40 cm) for men and women, respectively, predispose to OSA. Neck circumference is likely to remain an independent predictor of OSA even after accounting for BMI, and may even provide stronger correlation than BMI with certain disease severity measures, such as AHI and Spo2 nadir, in OSA patients [25]. Indeed, a neck circumference > 43 cm has been found to be associated with moderate and severe OSA, regardless BMI in the present study, confirming the key role of this anthropometric parameter in the evaluation of patients with suspected OSA.

Among symptoms and signs, excessive daytime sleepiness is certainly the one most well-recognized and associated with OSA [27], being reported by 15% to 50% of people with OSA in programs of general population screening [4], and up to 90% of patients with OSA referred to sleep clinics and caused by the repetitive disrupting of sleep during obstructive events [28]. In the present study, the excessive daytime sleepiness, objectively evaluated with the ESS, confirmed its strong association with OSA. However, it is important to note that not all patients affected by OSA are sleepy. Indeed, several cluster analyses found that only part of the OSA population may suffer from excessive daytime sleepiness, while other OSA patients may manifest insomnia or even no particular symptoms at all, making the diagnostic approach of these patients challenging [29]. Furthermore, it is important to aknowledge the role of nocturia in the association with OSA. Nocturia is usually more prevalent among older people, especially men, because of the increasing prevalence of both prostatic diseases and heart failure in these subjects. However it is also very common in OSA patients. A population study reported nocturia (at least 2 times per night) in 37.4% of individuals with an AHI of at least 20 events/hour [30]. Nocturia in OSA is triggered by the negative intrathoracic pressure resulting from closed upper airways, that causes distention of the right atrium and ventricle, which represents the stimulus for the release of

natriuretic peptides, leading to both inhibited secretion of antidiuretic hormone and aldosterone, resulting in increased diuresis [31]. Therefore, in a patient complaining of nocturia, especially if young, a sleep study should be advised. Indeed, the present study confirmed the key role of nocturia in the association with OSA, especially severe OSA. The relationship between arterial hypertension and OSA has been deeply evaluated and is well-recognized [32]. Blood pressure increase, initially at night and then sustained over 24 hours, and the consequent hypertension-mediated organ damage in OSA patients, recognizes several underlying factors, mostly united by the intermittent closure of the upper airway leading to intermittent hypoxia: the autonomic derangement, with increased sympathetic activity and alteration of both chemo- and baroreflexes, the changes in sleep structure, the intrathoracic pressure swings leading to an altered cardiac activity, the activation of the renin-angiotensin-aldosterone system with sodium retention and vasoconstriction, the oxidative stress and the endothelial disfunction leading to vascular remodeling and increased arterial stiffness, the low-grade systemic chronic inflammation, the metabolic disfunctions (mainly glucose and lipid dysmetabolism) [33–36]. Cross-sectional population-based studies found a higher prevalence of hypertension in OSA patients compared with controls, even after adjusting for age and body weight, in whom nearly half of patients with OSA had coexisting hypertension [37,38]. An increased likelihood of hypertension with increasing OSA severity was also found by several studies. Indeed, the investigators of the Sleep Heart Health Study found that prevalence of hypertension increased with increasing OSA severity, being 59%, 62%, and 67% in mild, moderate, and severe sleep apnea, respectively [38]. Furthermore, prospective longitudinal studies found that moderate-to-severe OSA was an independent risk factor for incident hypertension in patients who were normotensive at baseline [37,39]. Indeed, patients with

moderate-to-severe OSA enrolled in the Wisconsin Sleep Cohort Study had a three-fold higher risk of developing hypertension compared to those without OSA [37]. Even milder OSA has been found to be an independent risk factor for incident hypertension in middle-aged patients [40]. Patients affected by OSA have usually high prevalence of resistant hypertension, masked hypertension, and nondipping nocturnal blood pressure pattern [41]. When the physiological nocturnal BP reduction, known as the "dipping phenomenon" [42] is lacking, there is an established higher risk of adverse cardiovascular outcomes in both hypertensive and general population [43,44]. Studies with 24-hour ABPM found high prevalence of nondipping nocturnal blood pressure pattern, defined as a lack of drop in blood pressure at night rest of at least 10%, in OSA [45,46]. Furthermore, finding a non-dipping blood pressure pattern is highly suggestive of OSA, regardless of symptoms, and it is associated with an increased incidence of cardiovascular events regardless of blood pressure value [47]. Indeed, being a non-dipper, even if normotensive, may be associated with a more than two-fold higher risk of cardiovascular events compared with a dipper [48]. Moreover, patients with OSA and a nondipping blood pressure pattern are more likely to have cardiovascular events, even in the absence of diagnosed hypertension [49]. Therefore, OSA should always be suspected in subjects with nocturnal hypertension or non-dipping/reverse dipping patterns at a 24-hour ABPM [20,50], and on the other hand, a 24-hour ABPM should be performed to adequately assess the BP profile in patients diagnosed with OSA [51].

Not by chance, in the present study in OSA patients, arterial hypertension was highly prevalent and was independently associated with the presence of moderate OSA. Furthermore, the non-dipping/reverse dipping pattern at ABPM was independently associated with severe OSA, confirming the findings of previous published literature.

There is also a well-recognized association between OSA and both subclinical [35] and overt cardiovascular disease [25] that has been found in multiple uncontrolled longitudinal observational studies in whom severe untreated OSA has been shown to be a risk factor for cardiovascular disease and mortality [12,52]. The severity of hypoxaemia may be a key determinant of cardiovascular disease in OSA patients [53]. In the Sleep Heart Health Study, the risk of cardiovascular disease with OSA in middle-aged community-based adults was related to the severity of oxygen desaturations [54]. To date, the grading of OSA severity still relies on the number of obstructive events per hour of sleep. However, the degree of hypoxemia is likely to better reflect both the actual severity of the disease and the risk of complications associated to or caused by OSA. Indeed in the present study, the most used oximetry parameters (ODI, mean SpO2, nadir SpO2, mean of desaturations and T90) were grouped within a single variable (Oxy-score) using factor analysis. Oxy-score was found to be associated with cardiovascular organ damage, in particular hypertensive heart disease, regardless oAHI, in multivariate analisys. The association between OSA and hypertensive heart disease has already been evaluated and confirmed by metanalytic data [55]. Furthermore, cluster analysis studies have found that hypoxemic feature of OSA are able to detect a particular phenotype at higher risk for cardiovascular morbidity and mortality among patients with moderate to severe OSA, beyond the AHI [56], stressing the concept that not only the mere number of obstructive events should be taken into account when grading the OSA, but also, and likely mostly, the oximetry parameters.

Study limits

The main strengths of this study were the large sample, as well as the large amount of data analyzed, which made it possible to identify independet associations between moderate and severe OSA and several clinical parameters. However, the present study has also several limitations that must be taken into account. First of all, the observational nature of the study, a cross-sectional study in which no cause-effect link can be determined between the associations found, but only hypothetical speculations, although confirmed by an extensive published literature, can be made about the possible underlying mechanisms. Secondly, the incompleteness of some data, in particular those concerning ambulatory blood pressure parameters, has certainly limited the ability of this study to identify possible associations. However, having found such independent associations between oximetry parameters and hypertensive heart disease even in a smaller subgroup of patients, confirms the relevance of nocturnal intermittent hypoxemia as a major contributor of cardiovascular organ damage in OSA. Finally, performing a polygraphy, instead of a full polysomnography, has probably led to possible underestimation of the severity of respiratory sleep disorders in the sample analyzed, since polygraphy is usually a less accurate, albeit validated, diagnostic test for OSA.

CONCLUSION

The present study confirms the role of several clinical features, such as neck circumference among the body characteristics, nocturia and excessive daytime sleepiness among the daytime and nighttime symptoms and signs, arterial hypertension and a non-dipper/reverse dipper blood pressure pattern at ABPM among the comorbidities, in the association with moderate and severe OSA. Furthermore, it also highlights the association between oximetry parameters and cardiovascular organ damage, especially hypertensive heart disease, regardless of the oAHI, thus providing interesting insights for future prospective studies aimed at further investigating the role of oximetry parameters in determining both the severity of OSA and the risk of OSA-related cardiovascular disease.

REFERENCES

1. Benjafield A V, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med. 2019;7:687–98.

2. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013;177:1006–14.

3. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. J Thorac Dis. 2015;7:1311–22.

4. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med. 2015;3:310–8.

5. Malhotra A, White DP. Obstructive sleep apnoea. Lancet (London, England). England; 2002;360:237–45.

6. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. United States; 1993;328:1230–5.

7. Tregear S, Reston J, Schoelles K, Phillips B. Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis. J Clin sleep Med JCSM Off Publ Am Acad Sleep Med. 2009;5:573–81.

8. Kerner NA, Roose SP. Obstructive Sleep Apnea is Linked to Depression and Cognitive Impairment: Evidence and Potential Mechanisms. Am J Geriatr psychiatry Off J Am Assoc Geriatr Psychiatry. 2016;24:496–508.

9. Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. Nat Rev Dis Prim. England; 2015;1:15015.

10. McNicholas WT, Bonsigore MR. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J. England; 2007;29:156–78.

11. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med. United States; 2005;353:2034–41.

12. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010;122:352–60.

13. O'Donnell C, O'Mahony AM, McNicholas WT, Ryan S. Cardiovascular manifestations in obstructive sleep apnea: current evidence and potential mechanisms. Polish Arch Intern Med. Poland; 2021;131:550–60.

14. Insalaco G, Fanfulla F, Benassi F, Dal Farra F, De Michelis C, Patruno V, Sacco C, Sanna A, and Braghiroli A, on behalf of AIPO. 2011. Raccomandazioni per la diagnosi e cura dei disturbi respiratori nel sonno. Milano, Italy. 98 p. ISBN: 978-88-97334-00-2.

15. Johns MW. Sleepiness in different situations measured by the Epworth Sleepiness Scale. Sleep. United States; 1994;17:703–10.

16. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. United States; 1999;131:485–91.

17. Nuckton TJ, Glidden D V, Browner WS, Claman DM. Physical examination: Mallampati score as an independent predictor of obstructive sleep apnea. Sleep. United States; 2006;29:903–8.

18. Giulietti F, Filipponi A, Rosettani G, Giordano P, Iacoacci C, Spannella F, et al.

Pharmacological Approach to Smoking Cessation: An Updated Review for Daily Clinical Practice. High Blood Press. Cardiovasc. Prev. 2020.

19. Martin SS, Blaha MJ, Elshazly MB, Toth PP, Kwiterovich PO, Blumenthal RS, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. JAMA. 2013;310:2061–8.

20. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. England; 2018;39:3021–104.

21. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. England; 2020;41:111–88.

22. Omboni S, Palatini P, Parati G. Standards for ambulatory blood pressure monitoring clinical reporting in daily practice: Recommendations from the Italian Society of Hypertension. Blood Press Monit. 2015;

23. Fedecostante M, Spannella F, Giulietti F, Espinosa E, Dessì-Fulgheri P, Sarzani R. Associations between body mass index, ambulatory blood pressure findings, and changes in cardiac structure: relevance of pulse and nighttime pressures. J Clin Hypertens (Greenwich). United States; 2015;17:147–53.

24. Balietti P, Spannella F, Giulietti F, Rosettani G, Bernardi B, Cocci G, et al. Ten-year changes in ambulatory blood pressure: The prognostic value of ambulatory pulse pressure. J Clin Hypertens. 2018;

25. Yeghiazarians Y, Jneid H, Tietjens JR, Redline S, Brown DL, El-Sherif N, et al. Obstructive Sleep Apnea and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. United States; 2021;144:e56–67.

26. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA. United States; 2000;284:3015–21.

27. Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. JAMA. United States; 2020;323:1389–400.

28. Guilleminault C, Black JE, Palombini L, Ohayon M. A clinical investigation of obstructive sleep apnea syndrome (OSAS) and upper airway resistance syndrome (UARS) patients. Sleep Med. Netherlands; 2000;1:51–6.

29. Ye L, Pien GW, Ratcliffe SJ, Björnsdottir E, Arnardottir ES, Pack AI, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. Eur Respir J. 2014;44:1600–7.

30. Martin SA, Appleton SL, Adams RJ, Taylor AW, Catcheside PG, Vakulin A, et al. Nocturia, Other Lower Urinary Tract Symptoms and Sleep Dysfunction in a Community-Dwelling Cohort of Men. Urology. United States; 2016;97:219–26.

31. Barbara A. Phillips, Chapter 152 - Obstructive Sleep Apnea in Older Adults, Editor(s): Meir Kryger, Thomas Roth, William C. Dement, Principles and Practice of Sleep Medicine (Sixth Edition), Elsevier, 2017, Pages 1496-1502.e5, ISBN 9780323242882, https://.

32. Torres G, Sánchez-de-la-Torre M, Barbé F. Relationship Between OSA and Hypertension. Chest. United States; 2015;148:824–32.

33. Lombardi C, Pengo MF, Parati G. Systemic hypertension in obstructive sleep apnea. J Thorac Dis. 2018;10:S4231–43.

34. Parati G, Lombardi C, Hedner J, Bonsignore MR, Grote L, Tkacova R, et al. Recommendations for the management of patients with obstructive sleep apnoea and hypertension. Eur Respir J. England; 2013;41:523–38.

35. Cuspidi C, Tadic M, Gherbesi E, Sala C, Grassi G. Targeting subclinical organ damage

in obstructive sleep apnea: a narrative review. J Hum Hypertens. England; 2021;35:26–36.
36. Del Pinto R, Grassi G, Ferri C, Pengo MF, Lombardi C, Pucci G, et al. Diagnostic and Therapeutic Approach to Sleep Disorders, High Blood Pressure and Cardiovascular Diseases: A Consensus Document by the Italian Society of Hypertension (SIIA). High blood Press Cardiovasc Prev Off J Ital Soc Hypertens. 2021;28:85–102.
37. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. United States; 2000;342:1378–84.
38. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA. United States; 2000;283:1829–36.
39. Marin JM, Agusti A, Villar I, Forner M, Nieto D, Carrizo SJ, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. JAMA. 2012;307:2169–76.
40. Vgontzas AN, Li Y, He F, Fernandez-Mendoza J, Gaines J, Liao D, et al. Mild-to-moderate sleep apnea is associated with incident hypertension: age effect. Sleep. 2019;42.
41. Parati G, Ochoa JE, Bilo G, Mattaliano P, Salvi P, Kario K, et al. Obstructive sleep apnea syndrome as a cause of resistant hypertension. Hypertens Res. England; 2014;37:601–13.
42. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. Lancet (London, England). England; 1988. p. 397.
43. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. Hypertens (Dallas, Tex 1979). United States; 1994;24:793–801.

44. Boggia J, Li Y, Thijs L, Hansen TW, Kikuya M, Björklund-Bodegård K, et al. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. Lancet (London, England). England; 2007;370:1219–29.

45. Ancoli-Israel S, Stepnowsky C, Dimsdale J, Marler M, Cohen-Zion M, Johnson S. The effect of race and sleep-disordered breathing on nocturnal BP "dipping": analysis in an older population. Chest. United States; 2002;122:1148–55.

46. Loredo JS, Ancoli-Israel S, Dimsdale JE. Sleep quality and blood pressure dipping in obstructive sleep apnea. Am J Hypertens. United States; 2001;14:887–92.

47. Crinion SJ, Ryan S, Kleinerova J, Kent BD, Gallagher J, Ledwidge M, et al. Nondipping Nocturnal Blood Pressure Predicts Sleep Apnea in Patients With Hypertension. J Clin sleep Med JCSM Off Publ Am Acad Sleep Med. 2019;15:957–63.

48. Hermida RC, Ayala DE, Mojón A, Fernández JR. Blunted sleep-time relative blood pressure decline increases cardiovascular risk independent of blood pressure level--the "normotensive non-dipper" paradox. Chronobiol Int. England; 2013;30:87–98.

49. Sasaki N, Ozono R, Edahiro Y, Ishii K, Seto A, Okita T, et al. Impact of non-dipping on cardiovascular outcomes in patients with obstructive sleep apnea syndrome. Clin Exp Hypertens. England; 2015;37:449–53.

50. Pucci G, Fiorenzano G, Schillaci G. Obstructive sleep apnea and reverse dipping: the bad companions. J. Hypertens. England; 2014. p. 1964–6.

51. Parati G, Lombardi C, Hedner J, Bonsignore MR, Grote L, Tkacova R, et al. Position paper on the management of patients with obstructive sleep apnea and hypertension: joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (COoperation in Scientific . J Hypertens. England; 2012;30:633–46.

52. Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet (London, England). England; 2005;365:1046–53.

53. Turnbull CD. Intermittent hypoxia, cardiovascular disease and obstructive sleep apnoea. J Thorac Dis. 2018;10:S33–9.

54. Punjabi NM, Newman AB, Young TB, Resnick HE, Sanders MH. Sleep-disordered breathing and cardiovascular disease: an outcome-based definition of hypopneas. Am J Respir Crit Care Med. 2008;177:1150–5.

55. Cuspidi C, Tadic M, Sala C, Gherbesi E, Grassi G, Mancia G. Obstructive sleep apnoea syndrome and left ventricular hypertrophy: a meta-analysis of echocardiographic studies. J Hypertens. England; 2020;38:1640–9.

56. Labarca G, Jorquera J, Dreyse J, Salas C, Letelier F. Hypoxemic features of obstructive sleep apnea and the risk of mortality: a cluster analysis. Sleep Breath. Germany; 2021;25:95–103.

Table 1. General characteristics of the entire study population and according to age and sex.

Clinical characteristics	Study population (n° 618)	Age < 65 years (n° 357)	Age ≥ 65 years (n° 261)	p	Males (n° 448)	Females (n° 170)	p
Age (years)	61.0±13.6	51.7±9.2	73.8±6.4	<0.001	60.4±13.8	62.4±13.0	0.106
Sex (females)	27.5%	24.9%	31.0%	0.093	-	-	-
BMI (kg/m^2)	31.4±6.0	31.5±6.3	31.3±5.7	0.791	30.9±5.6	32.8±6.9	**0.001**
OW/OB	90.3%	90.2%	90.4%	0.926	90.0%	91.2%	0.647
OB	54.4%	55.2%	53.3%	0.635	51.8%	61.2%	**0.036**
Waist circumference (cm)	110.1±14.5	109.8±15.0	110.4±13.9	0.633	111.4±14.1	106.8±14.9	**0.001**
Neck circumference (cm)	41.8±4.1	41.7±4.1	42.0±4.0	0.395	43.0±3.6	38.7±3.8	**<0.001**
Mallampati (class III-IV)	91.4%	91.6%	91.2%	0.861	92.8%	87.9%	0.080
Macroglossia	81.0%	78.3%	84.1%	0.107	84.2%	73.0%	**0.004**
Uvula and soft palate enlargement	75.9%	74.1%	78.0%	0.323	77.1%	73.0%	0.345
Ogival palate	7.0%	9.2%	4.4%	**0.039**	7.2%	6.4%	0.773

Tonsillar hypertrophy	9.6%	11.8%	7.0%	0.076	10.0%	8.5%	0.605
Berlin Questionnaire (high risk)	87.9%	85.7%	90.8%	0.056	86.2%	92.4%	**0.035**
ESS	6.8±3.7	6.9±3.8	6.6±3.5	0.342	6.5±3.6	7.4±3.8	**0.005**
ESS > 10	14.4%	15.1%	13.4%	0.566	12.6%	19.2%	**0.040**
Lifestyle habits and comorbidities							
Sedentary lifestyle	79.6%	79.1%	80.1%	0.784	79.1%	80.7%	0.686
Smoking habit	62.0%	59.9%	64.5%	0.299	67.3%	49.0%	**<0.001**
COPD/asthma	21.7%	13.3%	31.4%	**<0.001**	21.8%	21.4%	0.933
Chronic Insomnia	23.3%	23.6%	23.0%	0.883	18.3%	35.7%	**<0.001**
Anxiety/Depression	20.2%	18.3%	22.6%	0.236	14.9%	33.6%	**<0.001**
Arterial hypertension	77.7%	68.1%	88.9%	**<0.001**	78.5%	75.7%	0.502
Impaired glucose metabolism	46.1%	40.7%	51.7%	**0.036**	48.4%	40.6%	0.172
T2DM	23.9%	18.8%	29.6%	**0.005**	23.0%	24.2%	0.782
Dyslipidemia	78.7%	71.2%	87.5%	**<0.001**	79.8%	76.1%	0.372

Hypertensive heart disease	69.9%	53.8%	88.2%	**<0.001**	71.9%	65.1%	0.162
CAD	15.3%	7.6%	24.2%	**<0.001**	18.1%	8.5%	0.008
TIA/Stroke	6.7%	2.3%	11.9%	**<0.001**	6.9%	6.4%	0.864
CHF	10.4%	3.0%	18.9%	**<0.001**	9.1%	13.6%	0.147
AFib	11.7%	5.7%	18.6%	**<0.001**	12.6%	9.3%	0.301
Permanent Pacemaker	3.7%	0.8%	7.1%	**<0.001**	4.3%	2.1%	0.253
CKD	11.5%	4.6%	19.5%	**<0.001**	12.9%	7.9%	0.114
PAD	63.8%	46.9%	83.4%	**<0.001**	64.2%	62.8%	0.762
GERD	30.5%	30.8%	30.1%	0.865	26.6%	40.0%	**0.004**
Dysthoyroidism	7.4%	4.9%	10.2%	**0.027**	5.2%	12.9%	**0.003**
BPH	20.0%	9.5%	32.3%	**<0.001**	-	-	
Chronic upper-airway disease	14.1%	17.5%	10.2%	**0.021**	15.2%	11.4%	0.281
Tonsillectomy	14.9%	16.0%	13.7%	0.486	14.0%	17.1%	0.384
Nighttime and daytime symptoms and signs							

Habitual snoring	94.3%	95.4%	92.9%	0.232	94.6%	93.6%	0.672
Witnessed breathing pauses	72.8%	71.9%	73.9%	0.615	77.7%	60.7%	**<0.001**
Subjective excessive daytime sleepiness	49.1%	51.7%	46.0%	0.209	45.6%	57.9%	**0.014**
Choking	44.0%	44.1%	43.8%	0.947	44.1%	43.6%	0.911
Morning dry mouth	80.0%	78.3%	81.9%	0.331	78.2%	84.3%	0.130
Morning headache	22.7%	27.4%	17.3%	**0.008**	16.9%	37.1%	**<0.001**
Nocturia	59.9%	45.2%	77.0%	**<0.001**	61.3%	56.4%	0.319
Night sweats	18.4%	23.6%	12.4%	0.001	16.6%	22.9%	0.108
Attention/ concentration/ memory impairment	40.7%	36.9%	45.1%	0.064	38.4%	46.4%	0.102
Witnessed limb movements	6.3%	5.3%	7.5%	0.320	4.8%	7.4%	0.205
Blood pressure parameters							

Office SBP (mmHg)	141.0±14.4	140.5±13.9	141.4±14.9	0.610	141.4±14.2	140.0±14.9	0.446
Office DBP (mmHg)	81.7±10.9	86.1±9.7	77.7±10.3	**<0.001**	82.2±11.3	80.4±9.8	0.209
Office HR (bpm)	69.9±11.4	70.9±11.9	68.9±10.9	0.136	69.4±11.9	70.9±10.3	0.315
Office PP (mmHg)	59.2±13.0	54.4±10.5	63.5±13.6	**<0.001**	59.1±12.7	59.6±13.8	0.774
Office BP control	12.5%	11.3%	13.5%	0.571	11.2%	15.3%	0.343
24-hour SBP* (mmHg)	132.3±13.0	131.7±13.0	133.3±13.0	0.399	132.1±13.1	132.8±12.7	0.776
24-hour DBP* (mmHg)	78.3±9.7	81.5±8.4	73.0±9.5	**<0.001**	79.2±9.6	75.4±9.8	**0.021**
24-hour PP* (mmHg)	54.1±11.4	50.2±9.0	60.3±12.2	**<0.001**	52.9±10.9	57.3±12.3	**0.022**
24-hour BP* control	29.9%	25.9%	36.6%	0.119	30.0%	29.8%	0.978
Daytime SBP* (mmHg)	134.7±13.3	135.1±13.1	134.0±13.7	0.600	134.8±13.4	134.4±13.2	0.886
Daytime DBP* (mmHg)	80.5±10.4	84.3±8.6	74.2±10.1	**<0.001**	81.5±10.3	77.5±10.3	**0.024**
Daytime PP* (mmHg)	54.2±11.2	50.8±9.1	59.9±12.2	**<0.001**	53.3±10.9	56.9±11.8	0.055
Daytime BP* control	41.0%	36.2%	48.6%	0.093	41.1%	40.4%	0.932
Nighttime SBP* (mmHg)	127.0±15.6	124.5±15.6	131.1±14.8	**0.005**	129.4±14.8	126.2±15.8	0.220
Nighttime DBP* (mmHg)	73.5±10.1	75.5±9.8	70.3±9.7	**0.001**	74.1±10.1	71.9±9.9	0.196
Nighttime PP* (mmHg)	53.4±12.5	49.0±9.6	60.8±13.1	**<0.001**	52.1±11.9	57.5±13.3	**0.009**
Nighttime BP control*	20.3%	19.8%	21.1%	0.830	21.4%	17.0%	0.516

Night-to-day ratio SBP*	0.94±0.08	0.92±0.07	0.98±0.08	**<0.001**	0.94±0.08	0.96±0.07	**0.043**
Night-to-day ratio DBP*	0.92±0.09	0.90±0.08	0.95±0.09	**<0.001**	0.91±0.09	0.93±0.08	0.229
Non-dipper/reverse-dipper pattern*	77.5%	70.9%	85.7%	**0.036**	75.0%	84.2%	0.245
Laboratory parameters							
Glycaemia (mg/dl)	101 (91-115)	98 (90-110)	104 (93-122)	**0.001**	101 (91-116)	101 (91-115)	0.925
Tc (mg/dl)	190.4±39.3	200.1±38.3	181.0±38.1	**<0.001**	188.0±40.6	196.7±35.3	0.069
HDLc (mg/dl)	46.1±13.2	45.9±13.8	46.4±12.6	0.742	44.6±12.9	50.1±13.1	**0.001**
Non-HDLc (mg/dl)	144.9±38.4	155.0±35.8	135.2±38.3	**<0.001**	144.0±39.9	147.6±34.2	0.441
Triglycerides (mg/dl)	113.5 (87-157.3)	121 (92-188)	104 (80-146)	**0.002**	116 (87-156)	107 (92-162)	0.822
LDLc	120.0±35.5	128.9±34.6	111.5±34.2	**<0.001**	119.4±36.9	121.8±31.6	0.560
LDLc control (not met)	91.4%	89.2%	93.6%	0.140	89.8%	95.7%	0.080
Creatinine (mg/dl)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	1.0 (0.8-1.2)	**0.011**	1.0 (0.9-1.1)	0.8 (0.7-0.9)	**<0.001**
eGFR (ml/min/1.73m^2)	80.5±20.6	86.7±17.5	74.1±21.7	**<0.001**	82.2±20.6	76.5±20.2	**0.010**
eGFR < 60 ml/min/1.73m^2	15.9%	5.3%	27.0%	**<0.001**	14.3%	19.7%	0.173
TSH µUI/ml	2.1 (1.2-2.8)	2.1 (1.3-2.8)	2.1 (1.1-2.9)	0.662	2.0 (1.1-2.7)	2.3 (1.2-3.0)	0.194

Cardiovascular drug therapy							
ACE-I/ARB	61%	51.1%	72.7%	**<0.001**	60.9%	61.2%	0.940
Diuretic	34.6%	23.4%	48.0%	**<0.001**	32.6%	39.5%	0.163
Dihydropyridine CCB	30.3%	26.1%	35.4%	**0.036**	33.7%	22.5%	**0.021**
Beta blocker	31.9%	23.8%	41.4%	**<0.001**	30.3%	35.7%	0.270
Antihypertensive treatment	71.9%	61.6%	84.5%	**<0.001**	71.5%	72.9%	0.776
TIS	1.2±1.1	1.0±1.1	1.4±1.1	**<0.001**	1.2±1.1	1.1±1.0	0.366
Statin	44.2%	29.0%	62.2%	**<0.001**	46.0%	40.0%	0.251
Anticoagulant	10.1%	3.4%	18.0%	**<0.001**	10.8%	8.5%	0.461
Antiplatelet	30.0%	16.9%	45.7%	**<0.001**	31.4%	26.9%	0.354

*Data available on 187 patients

Continuous variables were expressed as mean ± standard deviation, or as median and interquartile range if markedly skewed. Categorical variables were expressed as percentage. BMI: body mass index; OW/OB: overweight/obese; ESS: Epworth sleepiness scale; COPD: chronic obstructive pulmonary disease; T2DM: type 2 diabetes mellitus; CAD: coronary artery disease; TIA: transient ischemic attack; CHF: chronic heart failure; AFib: atrial fibrillation; CKD: chronic kidney disease; PAD: peripheral arterial disease; GERD: gastro-esophageal reflux disease; BPH: benign prostatic hyperplasia; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; PP: pulse pressure; Tc: total cholesterol; HDLc: high-density lipoprotein cholesterol; LDLc: low-density lipoprotein cholesterol eGFR: estimated glomerular filtration rate; TSH: thyroid-stimulating hormone; ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II type-1 receptor blocker; CCB: calcium-channel blocker; TIS: treatment intensity score (antihypertensive therapy).

Table 2. Polygraphic characteristics of the entire study population and according to age, sex and body mass index.

Polygraphic parameters*	Study population (n° 618)	Age < 65 years (n° 357)	Age ≥ 65 years (n° 261)	p	Males (n° 448)	Females (n° 170)	p	BMI < 30 kg/m^2 (n° 282)	BMI ≥ 30 kg/m^2 (n° 336)	p
AHI (events/hour)	30.8±20.9	30.0±22.4	31.9±18.6	0.260	32.9±21.9	25.3±16.8	**<0.001**	23.5±16.6	37.0±22.1	**<0.001**
oAHI (events/hour)	27.5±18.8	27.2±20.1	28.0±16.9	0.609	28.9±19.7	24.0±15.9	**0.002**	20.6±14.5	33.4±20.0	**<0.001**
oAHI ≥ 15	71.7%	68.6%	75.9%	**0.049**	74.3%	64.7%	**0.018**	55.0%	85.7%	**<0.001**
oAHI ≥ 30	35.8%	33.3%	39.1%	0.141	38.2%	29.4%	**0.043**	19.9%	49.1%	**<0.001**
cAHI (events/hour)	1.6±3.9	1.3±4.0	2.1±3.6	**0.013**	2.0±4.4	0.8±1.7	**<0.001**	1.6±3.2	1.7±4.4	0.776
CSB-CSA	1.8%	0.3%	3.8%	**0.001**	2.0%	1.2%	0.485	2.1%	1.5%	0.549
ODI (events/hour)	33.9±22.3	32.2±23.4	36.2±20.4	**0.026**	35.8±23.1	28.9±19.0	**<0.001**	25.5±17.7	40.9±23.3	**<0.001**
Nadir SpO2 (%)	77.1±9.2	78.2±9.3	75.7±8.9	**0.001**	76.8±9.4	78.0±8.8	0.156	80.1±7.5	74.7±9.8	**<0.001**
Mean SpO2 (%)	94 (92-95)	94 (93-96)	93 (91-94)	**<0.001**	94 (92-95)	94 (92-95)	0.186	94 (93-96)	93 (91-94)	**<0.001**

Mean of desaturations (%)	90 (86-91)	90 (87-92)	89 (86-90)	**<0.001**	90 (86-91)	90 (88-92)	**0.011**	90 (89-92)	89 (85-90)	**<0.001**
Severity of desaturations (moderate/severe)	45.8%	38.7%	55.6%	**<0.001**	47.8%	40.6%	0.110	31.2%	58.0%	**<0.001**
T90 (%)	5.2 (0.8-17.7)	3.2 (0.2-15.2)	8.7 (2.6-25)	**<0.001**	5.8 (0.9-19.6)	4.4 (0.5-14.4)	0.118	2.2 (0.2-8.8)	10.0 (2.2-27.0)	**<0.001**
T90 ≥ 30%	16.3%	12.3%	21.8%	**0.002**	16.7%	15.3%	0.664	7.1%	24.1%	**<0.001**
Supine position (%)	64.8±25.8	65.0±24.5	64.4±27.5	0.765	62.1±25.2	71.7±26.0	**<0.001**	63.3±25.6	66.0±25.9	0.204
Supine AHI/non-supine AHI	1.1 (0.6-2.1)	1.2 (0.6-2.3)	1.0 (0.6-1.9)	**0.044**	1.1 (0.6-2.1)	1.1 (0.6-2.1)	0.637	1.3 (0.7-2.7)	1.0 (0.7-1.8)	**<0.001**
pOSA	14.9%	17.8%	10.8%	**0.032**	16.1%	11.1%	0.183	21.7%	9.5%	**<0.001**

*All values are referred to the valid recording time of each examination.
Continuous variables were expressed as mean ± standard deviation, or as median and interquartile range if markedly skewed. Categorical variables were expressed as percentage.
BMI: body mass index; AHI: apnea-hypopnea index; oAHI: obstructive apnea-hypopnea index; cAHI: central apnea-hypopnea index; CSB-CSA: Cheyne-Stokes breathing-central sleep apnea; ODI: oxygen desaturation index; SpO2: peripheral oxygen saturation at pulse oximetry; T90: % of valid recording time spent with spO2 < 90%; pOSA: positional obstructive sleep apnea.

Table 3. Ambulatory blood pressure parameters according to OSA severity.

*Ambulatory blood pressure parameters**	oAHI < 15 (n° 23)	oAHI ≥ 15 (n° 164)	p	oAHI < 30 (n° 104)	oAHI ≥ 30 (n° 83)	p
24-hour SBP (mmHg)	129.5±12.1	132.7±13.1	0.266	131.9±13.0	132.8±13.0	0.617
24-hour DBP (mmHg)	78.7±9.1	78.2±9.9	0.834	79.2±9.6	77.1±9.9	0.148
24-hour PP (mmHg)	50.8±12.6	54.5±11.2	0.149	52.7±11.6	55.7±11.0	0.071
24-hour BP control	34.8%	29.3%	0.589	30.8%	28.9%	0.783
Daytime SBP (mmHg)	131.7±13.3	135.1±13.3	0.261	134.5±13.2	134.9±13.6	0.856
Daytime DBP (mmHg)	80.9±10.0	80.4±10.5	0.826	81.5±10.2	79.2±10.6	0.144
Daytime PP (mmHg)	50.8±12.6	54.7±11.0	0.124	53.1±11.6	55.7±10.6	0.116
Daytime BP control	47.8%	40.0%	0.475	44.8%	36.1%	0.233
Nighttime SBP (mmHg)	122.8±14.6	127.6±15.7	0.170	125.4±15.5	128.9±15.6	0.131
Nighttime DBP (mmHg)	73.6±9.4	73.5±10.2	0.964	73.9±9.9	73.1±10.4	0.589

Nighttime PP (mmHg)	49.2±12.1	54.0±12.4	0.079	51.6±12.1	55.8±12.5	**0.019**
Nighttime BP control	17.4%	20.7%	0.709	21.2%	19.3%	0.751
Night-to-day ratio SBP	0.9±0.1	0.9±0.1	0.598	0.9±0.1	1.0±0.1	**0.045**
Night-to-day ratio DBP	0.9±0.1	0.9±0.1	0.915	0.9±0.1	0.9±0.1	0.203
Dipping SBP	6.5±10.4	5.5±7.5	0.598	6.7±7.9	4.4±7.7	**0.045**
Dipping DBP	8.5±10.5	8.3±8.3	0.915	9.0±8.0	7.4±9.1	0.203
Non-dipper/ reverse-dipper pattern	75.0%	77.8%	0.802	65.8%	90.9%	**<0.001**

*Data available on 187 patients
Continuous variables were expressed as mean ± standard deviation, or as median and interquartile range if markedly skewed. Categorical variables were expressed as percentage.
oAHI: obstructive apnea-hypopnea index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure.

Table 4. Univariate analyses for predictors of moderate and severe OSA.

Variables	oAHI < 15 (n° 175)	oAHI ≥ 15 (n° 443)	p	OR	oAHI < 30 (n° 397)	oAHI ≥ 30 (n° 221)	p	OR
Age ≥ 65 years	36.0%	44.7%	**0.049**	1.4 (1.0-2.1)	40.1%	46.2%	0.141	1.3 (0.9-1.8)
Male sex	65.7%	75.2%	**0.018**	1.6 (1.1-2.3)	69.8%	77.4%	**0.043**	1.5 (1.0-2.2)
BMI ≥ 30 kg/m^2	27.4%	65.0%	**<0.001**	4.9 (3.3-7.2)	43.1%	74.7%	**<0.001**	3.9 (2.7-5.6)
Waist circumference >110 cm	21.1%	52.6%	**<0.001**	4.2 (2.5-6.9)	33.9%	63.9%	**<0.001**	3.5 (2.4-5.1)
Neck circumference > 43 cm	14.9%	57.1%	**<0.001**	7.6 (4.8-12.0)	31.6%	69.7%	**<0.001**	5.0 (3.5-7.1)
OW/OB	80.0%	94.4%	**<0.001**	4.2 (2.4-7.2)	86.4%	97.3%	**<0.001**	5.6 (2.4-13.3)
Mallampati (class III-IV)	78.2%	95.3%	**<0.001**	5.6 (2.9-10.8)	86.6%	99.0%	**<0.001**	14.6 (3.5-61.1)

Uvula and soft palate enlargement	66.4%	78.7%	**0.008**	1.9 (1.2-3.0)	73.9%	79.1%	0.194	1.3 (0.9-2.1)
Macroglossia	58.2%	87.6%	**<0.001**	5.1 (3.1-8.3)	72.9%	93.7%	**<0.001**	5.5 (2.9-10.4)
Berlin Questionnaire (high risk)	76.6%	92.3%	**<0.001**	3.7 (2.2-6.0)	84.1%	94.6%	**<0.001**	3.2 (1.7-6.2)
ESS > 10	5.9%	17.7%	**<0.001**	3.4 (1.7-6.8)	10.9%	20.7%	**0.001**	2.2 (1.4-3.4)
Arterial hypertension	61.8%	82.3%	**<0.001**	2.9 (1.8-4.6)	73.2%	84.7%	**0.003**	2.0 (1.3-3.3)
Impaired glucose metabolism	29.7%	50.3%	**0.002**	2.4 (1.4-4.2)	37.1%	59.1%	**<0.001**	2.5 (1.6-3.8)
Dyslipidemia	67.9%	81.9%	**0.002**	2.1 (1.3-3.5)	73.8%	86.3%	**0.001**	2.2 (1.4-3.7)
TIA/Stroke	3.6%	7.6%	0.141	2.2 (0.8-6.4)	4.3%	10.5%	**0.008**	2.6 (1.3-5.3)
PAD	47.2%	68.6%	**<0.001**	2.5 (1.6-3.8)	57.3%	73.9%	**<0.001**	2.1 (1.4-3.2)
Witnessed breathing pauses	58.2%	77.0%	**<0.001**	2.4 (1.5-3.8)	67.6%	81.1%	**0.001**	2.1 (1.3-3.2)

Subjective excessive daytime sleepiness	34.5%	53.3%	**0.001**	2.2 (1.4-3.4)	39.8%	63.7%	**<0.001**	2.7 (1.8-3.9)
Choking	33.6%	47.0%	**0.013**	1.8 (1.1-2.7)	40.1%	50.0%	**0.032**	1.5 (1.0-2.2)
Nocturia	40.9%	65.4%	**<0.001**	2.7 (1.8-4.2)	49.2%	76.8%	**<0.001**	3.4 (2.3-5.2)
Night sweats	13.6%	19.8%	0.143	1.6 (0.9-2.9)	15.1%	23.7%	**0.016**	1.8 (1.1-2.8)
Attention/ concentration/ memory impairment	39.1%	41.2%	0.697	1.1 (0.7-1.7)	36.1%	47.9%	**0.010**	1.6 (1.1-2.4)
Non-dipper/reverse-dipper pattern	75.0%	77.8%	0.802	1.2 (0.4-3.9)	65.8%	90.9%	**<0.001**	5.2 (2.0-13.6)

oAHI: obstructive apnea-hypopnea index; OR: odds ratio; BMI: body mass index; OW/OB: overweight/obese; ESS: Epworth sleepiness scale; TIA: transient ischemic attack; PAD: peripheral arterial disease.

Table 5. Stepwise logistic regression analyses for predictors of moderate and severe OSA.

Variables	oAHI ≥ 15*			oAHI ≥ 30**		
	Wald	OR (95% CI)	p	Wald	OR (95% CI)	p
BMI ≥ 30 kg/m^2	6.0	2.5 (1.2-5.2)	0.014	/	/	/
Neck circumference > 43 cm	7.1	3.0 (1.3-6.7)	0.008	12.8	4.5 (2.0-10.4)	<0.001
Macroglossia	12.8	4.2 (1.9-9.0)	<0.001	/	/	/
ESS > 10	3.9	5.4 (1.0-29.4)	0.049	/	/	/
Arterial hypertension	9.0	3.0 (1.5-6.0)	0.003	/	/	/
Witnessed breathing pauses	5.5	2.3 (1.2-4.5)	0.019	/	/	/
Subjective excessive daytime sleepiness	2.8	1.9 (1.0-3.8)	0.092	/	/	/
Nocturia	/	/	/	6.2	3.5 (1.3-9.3)	0.013
Attention/ concentration/ memory impairment	/	/	/	4.6	2.6 (1.1-6.0)	0.033
Non-dipper/reverse-dipper pattern	/	/	/	8.7	6.3 (1.9-21.4)	0.003

*All variables were available in 337 patients. **All variables were available in 126 patients. R^2=0.37 and 0.44, respectively,

oAHI: obstructive apnea-hypopnea index; OR: odds ratio; BMI: body mass index; ESS: Epworth sleepiness scale.

Table 6a. Associations between polygraphic parameters and cardiovascular organ damage.

Variables	HHD			PAD			CKD			Office PP ≥ 60 mmHg			24-h PP ≥ 55 mmHg		
	+	-	p	+	-	p	+	-	p	+	-	p	+	-	p
oAHI (events/hour)	31.4±18.7	24.4±18.1	**0.001**	31.3±18.9	25.3±18.2	**0.001**	29.2±15.0	28.9±18.5	0.899	31.8±19.1	28.1±18.9	0.104	34.9±20.5	29.3±17.9	**0.048**
ODI (events/hour)	39.5±22.1	29.4±21.5	**<0.001**	39.5±22.3	30.6±21.6	**<0.001**	38.0±19.2	35.8±22.2	0.454	40.9±22.9	33.9±21.0	**0.008**	43.1±24.7	34.3±19.8	**0.010**
Mean SpO2 (%)	93 (91-94)	94 (93-96)	**<0.001**	93 (91-94)	94 (93-96)	**<0.001**	93 (91-94)	93 (91-95)	0.112	93 (91-94)	94 (92-95)	**0.002**	93 (91-95)	94 (92-95)	0.141
Nadir SpO2 (%)	74.7±9.2	79.5±8.0	**<0.001**	74.8±9.1	78.5±8.7	**<0.001**	74.0±9.1	76.4±9.1	**0.049**	74.2±9.4	77.0±8.8	**0.011**	73.8±10.2	77.1±8.8	**0.019**
T90 (%)	10.5 (3.1-27.0)	1.9 (0.1-8.7)	**<0.001**	10 (3-25)	2.8 (0.2-11.7)	**<0.001**	12.5 (3.5-26.9)	7.0 (1.4-21.0)	**0.025**	12 (3-25)	7 (1-20)	**0.017**	10 (2-25)	7 (2-18)	0.196
Mean of desaturations (%)	89 (85-90)	90 (89-92)	**<0.001**	89 (85-90)	90 (88-92)	**<0.001**	89 (85-90)	89 (86-90)	0.400	89 (85-90)	89 (86-90)	0.087	89 (85-90)	90 (87-90)	0.127

Continuous variables were expressed as mean ± standard deviation, or as median and interquartile range if markedly skewed. Categorical variables were expressed as percentage. + and - are referred to the presence and the absence of the cardiovascular organ damage, respectively. HHD: hypertensive heart disease; PAD: peripheral arterial disease; CKD: chronic kidney disease; PP: pulse pressure; oAHI: obstructive apnea-hypopnea index; ODI: oxygen desaturation index; SpO2: peripheral oxygen saturation at pulse oximetry; T90: % of valid recording time spent with spO2 < 90%.

.

Table 6b. Associations between polygraphic parameters and cardiovascular events.

Variables	CAD			TIA/Stroke		
	+	-	p	+	-	p
oAHI (events/hour)	29.2±16.2	29.0±19.3	0.949	33.8±17.0	28.8±19.0	0.141
ODI (events/hour)	40.7±21.3	35.4±22.5	0.055	45.1±17.5	35.6±22.6	**0.019**
Mean SpO2 (%)	93 (90-94)	94 (92-95)	**0.001**	92 (91-94)	94 (91-95)	0.074
Nadir SpO2 (%)	72.9±9.8	76.8±9.0	**0.001**	74.5±7.5	76.3±9.3	0.284
T90 (%)	13 (4-37)	6 (1-18)	**0.001**	12 (3-24)	7 (1-20)	0.105
Mean of desaturations (%)	89 (85-90)	90 (86-91)	**0.001**	89 (85-90)	89 (86-91)	0.107

Continuous variables were expressed as mean ± standard deviation, or as median and interquartile range if markedly skewed. Categorical variables were expressed as percentage. + and - are referred to the presence and the absence of the cardiovascular event, respectively. CAD: coronary artery disease; TIA: transient ischemic attack; oAHI: obstructive apnea-hypopnea index; ODI: oxygen desaturation index; SpO2: peripheral oxygen saturation at pulse oximetry; T90: % of valid recording time spent with spO2 < 90%.

Table 7. Logistic regression for the association between Oxy-score and cardiovascular organ damage/cardiovascular events.

Variables	Model 1*		Model 2**	
	OR (95% CI)	p	OR (95% CI)	p**
Hypertensive heart disease	0.40 (0.29-0.56)	**<0.001**	0.44 (0.29-0.60)	**<0.001**
PAD	0.54 (0.42-0.69)	**<0.001**	0.64 (0.46-0.89)	**0.007**
CKD	0.90 (0.69-1.18)	0.452	1.00 (0.68-1.50)	0.965
Office PP ≥ 60 mmHg	0.77 (0.59-0.99)	**0.039**	0.84 (0.60-1.18)	0.320
24-hour PP ≥ 55 mmHg	0.72 (0.54-0.97)	**0.029**	0.84 (0.56-1.28)	0.417
CAD	0.71 (0.57-0.88)	**0.002**	0.57 (0.41-0.79)	**0.001**
TIA/Stroke	0.82 (0.60-1.13)	0.217	1.09 (0.67-1.77)	0.734

*Model 1: univariate analysis
**Model 2 adjusted for age, sex and oAHI (obstructive apnea-hypopnea index)
OR: odds ratio; PAD: peripheral arterial disease; CKD: chronic kidney disease; PP: pulse pressure; CAD: coronary artery disease; TIA: transient ischemic attack.

Table 8. Logistic regressions for the association between oAHI and hypertensive heart disease (fully adjusted model 1) and between Oxy-score and hypertensive heart disease (fully adjusted model 2) in patients with available ambulatory blood pressure monitoring (n° 187).

Variables	Model 1*			Model 2**		
	Wald	OR (95% CI)	p	Wald	OR (95% CI)	p
oAHI	4.3	1.03 (1.00-1.06)	**0.039**	0.1	1.00 (0.97-1.04)	0.759
Age	18.1	1.10 (1.05-1.14)	**<0.001**	15.1	1.09 (1.04-1.14)	**<0.001**
Sex	0.6	1.45 (0.58-3.62)	0.427	0.5	1.42 (0.56-3.60)	0.462
Smoking habit	0.4	1.30 (0.58-2.93)	0.524	0.0	1.00 (0.42-2.35)	0.991
T2DM	2.0	2.74 (0.69-10.89)	0.153	2.7	3.20 (0.80-12.84)	0.100
24-hour BPcontrol	14.4	0.18 (0.07-0.44)	**<0.001**	14.4	0.17 (0.07-0.42)	**<0.001**
BMI ≥ 30 kg/m2	2.2	1.97 (0.80-4.90)	0.142	1.1	1.65 (0.66-4.11)	0.287
Oxy-score	/	/	/	4.1	0.45 (0.21-0.98)	**0.044**

OR: odds ratio; oAHI: obstructive apnea-hypopnea index; T2DM: type 2 diabetes mellitus; BP: blood pressure; BMI: body mass index.

Figure 1. ROC curves for the association of obstructive apnea-hypopnea index (oAHI) and Oxy-score with hypertensive heart disease.

Variables	AUC	95% CI
oAHI	0.634	0.586-0.681
Oxy-score	0.700	0.653-0.744

p for comparison of ROC curves= 0,0053