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"Prevalence, characteristics and association of obstructive sleep apnea with blood pressure control in patients with resistant hypertension"

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ABSTRACT

Rationale: Obstructive sleep apnea (OSA) is associated with poor blood pressure (BP) control and resistant hypertension (RH). Nevertheless, studies assessing its prevalence, characteristics and association with BP control in RH patients are limited.

Objective: The aim of this multicenter study was to assess the prevalence of OSA in a large cohort of RH subjects and to evaluate the association of OSA with BP control.

Methods: We recruited consecutive RH subjects from 3 countries. A formal sleep test and blood pressure measurements, including 24-h ambulatory blood pressure monitoring (ABPM) were performed in all participants. .

Results: In total, 284 RH subjects were included in the final analysis. Of these, 83.5% (CI 95%; 78.7 to 87.3) had OSA (apnea-hypopnea index (AHI) ≥5 events/h); 31.7% (26.5 to 37.3) had mild OSA, 25.7% (21 to 31.1) had moderate OSA and 26.1% (21.3 to 31.5) had severe OSA. Patients with severe OSA had higher BP values than mild-moderate or non-OSA subjects. A greater effect was observed on the average nighttime BP, with an adjusted effect of 5.72 (1.08 to 10.35) mmHg in severe OSA compared to non-OSA participants. A dose-response association between the severity of OSA and BP values was observed. The prevalence of severe OSA was slightly higher in uncontrolled participants (adjusted OR 1.69 (0.97 to 2.99)) but was not statistically significant.

Conclusions: The present study confirms the high prevalence of OSA in RH participants. Furthermore, it shows a dose-response association between OSA severity and BP measurements, especially in the nighttime.

Clinical Trial Registration: NCT03002558

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TEXT

INTRODUCTION

Hypertension represents an important and prevalent cardiovascular risk factor and it is considered an important topic in public health[1–3]. Among all hypertensive phenotypes, resistant hypertension (RH) is considered to confer the highest cardiovascular risk[1–4]. Among all hypertensive subjects, the estimated prevalence of RH ranges from 12-15%[5–7].

RH is defined as blood pressure (BP) that remains above the goal in spite of the use of 3 different antihypertensive drugs including a diuretic, prescribed at the optimal dose or as those in whom require 4 or more medications for BP controll[8]. Patients with RH have the worst prognosis of all hypertensive patients, as they presented with the highest rates of target organ damage and cardiovascular events in long-term follow-up; these rates are estimated to be 50% higher than in patients with controlled hypertension[9–14].

Moreover, it has been described that among all RH patients, those who presented with uncontrolled BP on the 24-hour ambulatory blood pressure monitoring (ABPM) measurements are at a higher risk of experiencing cardiovascular events, especially those subjects with the masked phenotype (normal office BP measures but above the normal range on the 24-hour ABPM)[11,15].

Obstructive sleep apnea (OSA) is a disorder characterized by recurrent episodes of upper airway collapse that result in intermittent hypoxia, sleep fragmentation, intrathoracic negative pressure and the disruption of sleep architecture. OSA is associated with daytime symptoms, a decrease in the quality of life and an increase in morbidity and mortality from cardiovascular alterations [16,17]. The prevalence of OSA in middle-aged population is 24-26% in men and 17%-28% in women[18–20]. However, its prevalence increases in hypertensive subjects (30-80%) and previous studies have

indicated that it could reach 64-83% in patients with RH[1,12,21–23]; the prevalence of OSA has also been reported to be 100% in refractory hypertensive patients (hypertension that remains uncontrolled despite the administration of at least 5 antihypertensive drugs, preferably including a long-acting thiazide-like diuretic and a mineral-corticoid receptor antagonist)[24–26]. Beyond this, it has been described that OSA could be associated with poor BP control and its treatment with continuous positive pressure (CPAP) could be an effective means of controlling BP in this population[27–32].

Nevertheless, studies evaluating the prevalence of OSA in RH patients and its association with BP control are scarce. These studies have usually been single-centre studies, which limit the generalizability of their results. Therefore, the aim of this study was to assess the prevalence of OSA in a large cohort of RH participants, identify the clinical variables associated with severe OSA and evaluate the association of OSA with BP control. All these issues are particularly relevant considering that the traditional screening questionnaires for OSA are not useful in patients with RH[33].

MATERIAL AND METHODS

Study design and population

This is an ancillary study of the SARAH study (Long-term Cardiovascular Outcomes in Patients With RH and OSA With or Without Treatment With CPAP), which is a multicenter, international, prospective, observational cohort study (registered trial NCT03002558), evaluating the impact of OSA and continuous positive airway pressure (CPAP) treatment on cardiovascular outcomes (morbidity and mortality) in subjects with RH.

Briefly, the study included consecutive subjects aged between 18-75 years who were diagnosed with RH confirmed by 24-hour ABPM, as defined later (see Blood Pressure measurements). The exclusion criteria for the study were RH secondary to endocrinological cause (pheochromocytoma, Conn disease, Cushing´s Syndrome,

hyperparatiroidism), drug treatment (nonsteroidal anti-inflammatory drugs or cortisone, inmunodepressants) renal artery stenosis, aortic coarctation or intracranial tumours; life expectancy less than 1 year and current treatment with CPAP. Subjects were evaluated for participation in the study in 6 teaching hospitals in Spain, 1 in Singapore and 1 in Sao Paulo. The methodology of the SARAH trial is published elsewhere[34]. The ethics committee of each participating centre approved the study and all participants provided informed consent.

For the current study, we included 284 participants consecutively recruited between April 2016 and July 2018. Information regarding eligibility and exclusions is provided in Figure 1. We analysed the presence and severity of OSA in the RH subjects, their clinical characteristics and the association of OSA with BP control.

Based on the results obtained on the sleep test, participants were classified as non-OSA (apnea-hypopnoea index (AHI) < 5/h) or OSA. Moreover, OSA subjects were classified as having mild (AHI 5-14.9/ h), moderate (AHI 15-29.9/ h) or severe (AHI ≥ 30/ h) OSA. Based on the results of the ABPM, participants with RH were classified as having controlled (average 24-hour ambulatory BP < 130/80 mmHg) or uncontrolled (average 24-hour ambulatory BP ≥130/80 mmHg) RH.

Procedures

Baseline visit

At the initial visit, all participants completed a detailed medical interview regarding their sociodemographic characteristics, cardiovascular risk factors, cardiovascular disease and medication. Self-reported sleepiness (analysed by the Spanish version of the Epworth Sleepiness Scale) and anthropometric measures were also recorded.

Sleep evaluation

A sleep test, consisting of either a cardio-respiratory polygraphy or polysomnography, was performed in all included participants. Of all the subjects included, 250 underwent cardiorespiratory polygraphy and 34 underwent polysomnography. Approximately 84% of the sleep studies were performed using an Embletta® sleep monitor. The rest of the studies were performed using: Compumedics E. Profusion 3.4; Sibelmed Exea Serie 5; Philips Respironics Alice 6 LDx; Somnomedics. Somnoscreen plus Versión 2.7.0; and ApneaLink Resmed.

Apnea was defined as an interruption in or reduction of oronasal airflow ≥ 90% that lasted at least 10 seconds. An apnea was scored as obstructive when it was associated with continued or increased inspiratory effort. It was scored as mixed when there was a lack of inspiratory effort in the initial portion of the event followed by the resumption of inspiratory effort in the second portion of the event. Central apnea was scored when the apnea was associated with a lack of inspiratory effort throughout the entire period of absent airflow. Hypopnoea was defined as a 30% to 90% reduction in oronasal airflow for at least 10 seconds associated with oxygen desaturation of at least 4% or an arousal. The AHI was defined as the number of apnea and hypopnoea events per hour of recording or sleep depending on the study (cardio-respiratory polygraphy or polysomnography, respectively). CT90 was defined as the percentage of time with an oxygen saturation lower than 90%. The diagnosis of central sleep apnea was made when at least 50% of the respiratory events were without respiratory effort. Central sleep apnea diagnosis was not considered an exclusion criterion. OSA diagnosis and treatment recommendations were based on the guidelines of each country according to usual clinical practice[35].

Blood pressure measurements

Office BP and 24-hour ABPM measurements were performed in all participants at the beginning of the study. During the initial visit, office BP was obtained in all participants

256 according to the guidelines. Office BP was determined by the average of three
257 recordings of systolic and diastolic BP obtained at 5-minute intervals after subjects had
258 been seated on a chair with their feet on the floor and arms supported at heart level for
259 at least 5 minutes[36].
260 ABPM measurement was performed following international guidelines[36]. Before the
261 ABPM monitor was fitted, the BP was measured in both arms to determine whether
262 there were differences in BP between them. If there were differences, the cuff was
263 placed on the arm with the higher BP values. If there were no differences in BP values
264 between arms, the cuff was placed in the non-dominant arm to interfere as little as
265 possible in the daily activities of participants. All participants were instructed to perform
266 their usual activities during the test [37].
267 During ABPM, a BP measurement was taken every 20 minutes during the daytime and
268 every 30 minutes during the night. All recruited subjects were asked about their sleep
269 habits. The waking and sleeping periods were determined by the times that each
270 individual reported awakening and going to bed, respectively. ABPM recordings were
271 considered successful when the percentage of the measurements was > 70%, with at
272 least one measurement every hour. Data related to the average 24-hour ambulatory
273 BP, daytime and nighttime systolic BP (SBP) and diastolic BP (DBP) and heart rate
274 were recorded.
275 The monitors used were Spacelabs 90207/90217A devices (Spacelabs® Inc.
276 Richmond, Washington, United States), Mortara Ambulo 2400 (Milwaukee, EE.UU),
277 Microlife WatchBP (Microlife AG, Switzerland), and Dyna-MAPA (Cardios Sistemas
278 Coml. Indl. Ltda, Sao Paulo, Brasil)
279
280 The 24-hour ABPM criteria used to define RH were a BP that remained above the
281 target (average SBP ≥ 130 mmHg, average DBP ≥ 80 mmHg or both) in spite of the
282 use of three antihypertensive drugs (one of those should be a diuretic) or a BP in the
283 optimal range with 4 or more antihypertensive medications (therefore these participants

were included regardless of the BP values recorded during the ABPM). Subjects treated with three antihypertensive drugs who had normal ABPM measurements (<130/80 mmHg) were excluded from the study.

The circadian dipping pattern of each participant was established according to the dipping ratio (DR) which is the quotient between the nighttime mean arterial pressure (MAP) and the daytime MAP. According to the quotient obtained, subjects were classified as non-dippers if the DR was higher than 0.9 and dippers if it was ≤ 0.9.

Considering ABPM values, daytime hypertension was defined as at least 135/85 mmHg for the daytime average and at least 120/70 mmHg for the nighttime average.[36]

BP control was defined based on the ABPM measurements. Thus, participants were considered controlled when the average 24-hour ambulatory BP was < 130/80 mmHg and uncontrolled when average 24-hour ambulatory BP was ≥130/80 mmHg.

All participants maintained their prescribed antihypertensive treatment during office and ABPM measurements. To evaluate adequate compliance with the antihypertensive treatment, the Morisky [38] and Haynes [39] tests were assessed. Moreover, participants must have retrieved from the pharmacy more than 80% of their prescribed antihypertensive treatment.

Statistical analyses

With regard to descriptive statistics, the means (standard deviation) and medians (interquartile range) were estimated for quantitative variables with normal or nonnormal distributions, respectively. The absolute and relative frequencies were used for qualitative variables. The normality of the distribution was analysed using the Shapiro–Wilk test. The Agresti–Coull intervals[40] (95%CI) were generated for the prevalence estimations. The demographic and clinical data of the participants were compared among the OSA severity groups (non-OSA, mild-moderate and severe) using the

appropriate tests (ANOVA or Kruskal-Wallis) for quantitative variables and Fisher's exact test for qualitative variables. The p-value for trend was computed from the Spearman's rank correlation coefficient when the variable was continuous and χ^2 test for trend if it was categorical [41]. ABPM parameters were compared among OSA severity groups with the Kruskal-Wallis test. In addition, the comparison was evaluated by ANOVA with linear models adjusted by confounding factors (age, sex and body mass index) and an unadjusted linear model. Trend tests were conducted, treating OSA categories as an ordinal variable by using the median AHI of each category. The same analysis was carried out to evaluate the sleep parameters according to BP control. R statistical software, version 3.3.1, was used for all the analyses [42].

RESULTS

Cohort characteristics

In total, 284 subjects with RH were included. The main socio-demographic and clinical characteristics of the population are shown in Table 1. Briefly, the median age (IQR) was 64 (57.0; 69.0) years, and the participants were predominantly male gender and obese. The most prevalent co-morbidity was diabetes (129 patients; 46.9%).

Prevalence of OSA characteristics in RH patients

In the whole cohort, 83.5% (95%CI; 78.7 to 87.3) of the included participants had an AHI greater than or equal to 5 events/h. With regard to OSA severity, 31.7% (26.5 to 37.3) of participants had mild OSA, 25.7% (21 to 31.1) had moderate OSA and 26.1% (21.3 to 31.5) had severe OSA.

The OSA prevalence was slightly higher in males than in females (86.3% (80.8 to 90.4) versus 76% (65.8 to 84.3)), respectively. Moreover, the prevalence of severe OSA was more than twice as high in men as it was in women (30.4%vs 15%). A high body mass index was also associated with a higher prevalence of OSA (70.6% in normal weight, 77.5% in overweight and 88.5% in obese subjects) and severe OSA was more

prevalent by increasing weight (11.8% in normal weight, 16.7% in overweight and 33.3% in obese subjects). Among the participants with severe OSA (AHI≥30 events/h), there was a larger proportion of men and they had higher body mass index, waist circumference and neck circumference values than those with mild-moderate OSA.

Regarding the sleep parameters, the median AHI (IQR) was 16.6 (7.88; 30.2) events/hour and the median 4% oxygen desaturation index (IQR) was 11.6 (5.75; 23.1) per hour. The percentage of time with an oxygen saturation < 90% was 11% (2.20; 35.8). The median Epworth sleepiness scale score was 6 (4.00; 10.0). None of the included participants was diagnosed with central sleep apnea. More detailed information is provided in Table 1.

ABPM parameters stratified by OSA severity

In general, ABPM parameters increased as the severity of OSA increased (Figure 2) and a statistically significant dose-response association was found (p for trend in Table 2). Higher values for all average 24-hour ambulatory BP parameters, daytime and nighttime average ambulatory BP and the daytime and nighttime diastolic BP were observed in severe OSA than in non-OSA participants. The effect was greater on nocturnal blood pressure, with an adjusted effect on the average nighttime ambulatory BP of 5.72 (1.08 to 10.35) mmHg in severe OSA compared to non-OSA participants. The adjusted and unadjusted effects of OSA severity on ABPM parameters are detailed in Table 2.

Furthermore, the adjusted OR (95% CI) of having nocturnal hypertension in severe OSA group compared with the non-OSA group was 2.7 (1.15 to 6.43). There was no statistically significant difference in the proportion of non-dippers according to OSA severity (56.4% in mild-moderate OSA and 70.3% in severe OSA).

OSA prevalence in the different BP control groups

No significant differences in sleep parameters were observed between subjects with controlled or uncontrolled BP. More detailed information is provided in Table 3. Moreover, similar OSA prevalence was observed between the groups; however, the results show that severe OSA was slightly more prevalent in participants with uncontrolled RH than in participants with controlled RH, with an adjusted OR of 1.69 (0.97 to 2.99), although the difference is not statistically significant (e-Table 1).

DISCUSSION

The present multicenter study confirms that the prevalence of OSA in RH subjects is high. Moreover, it shows that there is a dose-response association between the severity of OSA and the blood pressure values observed, with greater effects on nighttime BP.

Our study shows that the total prevalence of OSA is 83.5%; the prevalence of mild OSA is 31.7%, the prevalence of moderate OSA is 25.7%, and the prevalence of severe OSA is 26.1%. This prevalence is probably underestimated because 34 subjects were excluded from the SARAH study because they were currently with CPAP treatment. Therefore, considering these subjects, the estimated OSA prevalence would be around 95.4%.

Data from previous studies already reported a high prevalence of OSA in RH subjects, nevertheless, it is difficult to compare results among studies due to different or unspecified criteria used to define hypopnea, the use of different AHI cutoff values to diagnose OSA and the use of different sleep tests as well.

Previous published studies, such as those by Logan et al[12] and Florczak et al[23] reported an OSA prevalence rates of 83% and 72% respectively. Nevertheless, these authors did not indicate the criteria used to define hypopnea, making a comparison difficult. Moreover, in the study by Logan et al[12] all participants included had refractory hypertension. Comparing our results with those of the studies that indicating the

oxygen desaturation criteria used, we observed that our results are consistent with those of Muxfeldt et al[22] who reported an OSA prevalence of 82.2 % using the same criteria to define hypopnea (at least 4% oxygen desaturation) and participants with similar characteristics to those included in our study. However, in Muxfeld's study, only polysomnography was performed. The prevalence reported by Pedrosa et al[1], who used polysomnography and a 3% oxygen desaturation criteria to define hypopnea, was 64%, which is lower than in our study. This could be related with to the fact that the subjects included were younger, and they used a more conservative cutoff value to diagnose OSA (AHI ≥15/h).

The prevalence of OSA was higher in men than in women, and severe OSA was twice as prevalent in males as in females. This male predominance had been previously described in the general population, hypertensive patients and RH[1,22]. Moreover, as described in previous studies, OSA presence and severity increased as BMI increased[1,12]. Moreover, our data also show that the most frequent comorbidity was diabetes, which has been strongly associated with antihypertensive drug resistance[8,43].

A dose-response association between OSA severity and BP values was found. OSA severity was related to worse BP control with higher values for all 24-hour ambulatory blood pressure variables, the average daytime BP, daytime diastolic BP, average nighttime BP and nighttime diastolic BP values. Moreover the prevalence of nocturnal hypertension was significantly greater in participants with severe OSA. It is important to highlight the association of OSA with high nighttime BP values because it has been previously demonstrated that nocturnal BP is a better risk predictor than the daytime BP, and an elevated nighttime BP has been associated with an increased risk of cardiovascular events and worse cardiovascular prognosis[11]. It has also been described that the circadian pattern provides additional prognostic information beyond that possible with just average 24-hour BP levels, and a non-dipping pattern has also been associated with worse cardiovascular outcomes [44,45].Our results are in line with those of Muxfeld[22], who described a worse nocturnal BP profile and a higher

prevalence of a non-dipping patterns in subjects with severe OSA than in those without severe OSA, although in our study this last factor did not reach statistical significance. Therefore, as previously described[22], our results already show that beyond age, gender and anthropometric characteristics, ABPM measurements could also be associated with OSA severity, especially nighttime measures. The results suggest that identifying underlying causes, such as OSA and treating them may be helpful when attempting to improve BP control, especially during the nighttime, and may suggest new treatment approaches beyond pharmacology. Nevertheless, further studies should address the impacts of OSA treatment on BP parameters and cardiovascular outcomes in the long term.

Although we found a high OSA prevalence and a dose-response association between the severity of OSA and blood pressure values, no differences in sleep parameters were observed between the controlled or uncontrolled RH groups; which were defined based on average 24-hour ambulatory BP. This could be related to the fact that the greatest impact of OSA on BP has been observed on nocturnal pressure and that the nighttime period only represents approximately one-third of the 24-hour. In addition, the results suggest that the decision to explore OSA in subjects with RH should not be based on the BP control parameters proposed in the hypertension guidelines and that it could be especially important to assess OSA in subjects with RH who have high BP values at nighttime even if they have values in the normal ranges for the 24-hour measurements.

The main strength of our study is its multicenter and international design, with the inclusion of a large number of patients with RH diagnosed based on ABPM measurements. Therefore, unlike other previous published studies, we only included subjects with true RH. Furthermore, unlike other studies, we used indirect methods to estimate treatment compliance and ensure that at least 80% of the antihypertensive treatment was retrieved from the pharmacy.

This study has some limitations that should be acknowledged. First, it has a cross-sectional design; thus, only associations and not causality should be inferred. Second, two different methods were used for OSA diagnosis; cardiorespiratory polygraphy and polysomnography. Both methods have been validated and are commonly implemented in clinical practice. Nevertheless the severity of OSA can be underestimated using cardiorespiratory polygraphy; therefore the mild-moderate and severe OSA participants may have been misclassified. Third, OSA prevalence may have been underestimated due to the exclusion of subjects who were undergoing CPAP treatment. However, an estimated prevalence including those subjects has been included. Fourth, the study included RH subjects, and the reported prevalence results should not be generalized to a population with less severe hypertension.

CONCLUSIONS

Our study confirms that RH subjects have a high prevalence of OSA and shows a dose-response association between OSA severity and blood pressure measurements. The results highlight the importance of identifying OSA in RH subjects to reduce its impact on blood pressure control through appropriate treatment.

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FIGURE LEGENDS

Figure 1: Flow diagram of the study

Abbreviations: ABPM= Ambulatory blood pressure monitoring; CPAP= Continuous positive airway pressure

Figure 2: Least squares means and 95% confidence intervals for the ABPM parameters according to OSA severity.

Abbreviations: ABPM= Ambulatory blood pressure monitoring; OSA= Obstructive sleep apnea

TABLES

Table 1. Characteristics of the study cohort stratified by OSA severity

	Global (n=284)	Non-OSA (n=47)	Mild-Moderate OSA (n=163)	Severe OSA (n=74)	p value for trend
Sociodemographic characteristics					
Age (years) -*Me[p25;p75]*-	64.0 [57.0;69.0]	61.0 [52.0;69.0]	65.0 [59.0;69.0]	63.0 [55.5;68.0]	0.892
Sex (male) -*n (%)*-	204 (71.8%)	28 (59.6%)	114 (69.9%)	62 (83.8%)	0.003
Tobacco use -*%*-					0.367
Current smoker	36 (13.2%)	8 (18.2%)	18 (11.5%)	10 (13.9%)	
Former smoker	109 (39.9%)	12 (27.3%)	69 (43.9%)	28 (38.9%)	
Non-smoker	128 (46.9%)	24 (54.5%)	70 (44.6%)	34 (47.2%)	
Anthropometric characteristics					
BMI (kg/m^2) -*$Me[p_{25};p_{75}]$*-	31.1 [28.2;34.1]	29.2 [27.0;32.6]	30.8 [27.6;33.4]	32.8 [29.9;35.1]	<0.001
Waist circumference (cm) -*Me[p25;p75]*-	105 [99.0;113]	100 [97.0;108]	103 [97.0;112]	109 [102;118]	<0.001
Abdominal circumference (increased) -n%-	144 (50.7%)	22 (46.8%)	77 (47.2%)	45 (60.8%)	0.009
Hip circumference (cm) -*Me[p25;p75]*-	107 [101;113]	106 [102;113]	106 [100;112]	108 [102;116]	0.108
Neck circumference (cm) -*Me[p25;p75]*-	41.0 [38.0;44.0]	40.5 [36.0;42.0]	41.0 [38.0;44.0]	42.0 [40.9;44.0]	<0.001
Clinical variables					
Diabetes (yes) -*n (%)*-	129 (46.9%)	17 (38.6%)	79 (50.0%)	33 (45.2%)	0.66
Dyslipidaemia (yes) -*n (%)*-	43 (15.7%)	8 (18.6%)	24 (15.2%)	11 (15.1%)	0.639
Stroke (yes) -*n (%)*-	5 (1.81%)	0 (0.00%)	4 (2.55%)	1 (1.37%)	0.729
Coronary heart disease (events) -*n (%)*-	38 (13.8%)	4 (9.09%)	26 (16.5%)	8 (10.8%)	0.969
Sleep parameters -*Me[p25;p75]*-					
Apnea-Hypopnea index (events/h)	16.6 [7.88;30.2]	2.80 [1.50;4.25]	14.1 [9.55;20.6]	44.3 [35.8;63.0]	<0.001
Hypopnea Index (events/h)	10.4 [4.60;20.2]	2.10 [0.90;3.45]	10.4 [5.95;15.9]	22.2 [10.2;30.9]	<0.001
Apnea Index (events/h)	5.50 [1.30;14.7]	0.60 [0.05;1.70]	4.40 [1.40;9.15]	28.2 [12.2;46.4]	<0.001
ODI 4%	11.6 [5.75;23.3]	2.60 [1.18;4.07]	11.5 [7.80;17.7]	38.0 [31.2;53.5]	<0.001
CT90 (%)	11.0 [2.20;35.8]	0.50 [0.00;3.40]	10.8 [2.62;25.7]	31.9 [13.0;47.1]	<0.001
Obstructive + mixed events (%)	83.0 [20.0;100]	50.0 [0.00;100]	92.5 [28.8;100]	79.0 [34.0;97.0]	0.394
Mean. O_2 saturation (%)	91.8 [90.0;93.1]	93.5 [92.0;94.1]	92.0 [90.5;93.0]	90.1 [89.2;92.0]	<0.001
Min. O_2 saturation (%)	80.0 [74.0;84.0]	86.0 [84.0;88.5]	81.0 [76.0;84.0]	72.5 [65.2;79.0]	<0.001
ESS	6.00 [4.00;10.0]	6.00 [4.00;9.00]	6.00 [4.00;10.0]	6.00 [4.00;10.0]	0.653

Abbreviations: BMI=Body mass index;ESS: Epworth sleepiness scale; ODI= Oxygen desaturation index; OSA=Obstructive sleep apnea; CT90= Percentage of time with an oxygen saturation lower than 90%. Note: Prevalence Non OSA(AHI<5); Mild (5≥AHI<15); Moderate (15≥AHI<30); Severe (30≥AHI). The apnea index is the total number of apneas per hour (including obstructive, mixed and central apneas). Obstructive+mixed events: percentage corresponding to obstructive and mixed apneas of the total number of apneas.

Table 2. Association of OSA severity with ABPM parameters

	Non-OSA (n=47)	Mild-Moderate OSA (n=163)	Severe OSA (n=74)	p value for trend
ABPM - average 24-h BP (mean SD) -mmHg-	93.2 (9.06)	93.3 (10.3)	96.0 (12.0)	0,108
Mean difference (95% CI)	0 (Ref)	0.1 (-3.41 to 3.61)	2.8 (-1.14 to 6.74)	0,0665
Adjusted mean difference (95% CI)	0 (Ref)	1.74 (-1.76 to 5.25)	**4.73 (0.71 to 8.76)**	**0,0139**
ABPM - 24-h systolic BP (mean SD) -mmHg-	**128 (12.6)**	**130 (15.1)**	**133 (17.0)**	**0,05**
Mean difference (95% CI)	**0 (Ref)**	**2.18 (-2.79 to 7.16)**	**5.38 (-0.23 to 10.98)**	**0,0513**
Adjusted mean difference (95% CI)	**0 (Ref)**	**2.52 (-2.59 to 7.63)**	**6.14 (0.22 to 12.05)**	**0,0361**
ABPM - 24-h diastolic BP (mean SD) -mmHg-	74.6 (9.21)	72.7 (10.2)	76.1 (11.1)	0,255
Mean difference (95% CI)	0 (Ref)	-1.89 (-5.24 to 1.47)	1.48 (-2.3 to 5.26)	0,0851
Adjusted mean difference (95% CI)	0 (Ref)	0.65 (-2.41 to 3.72)	**4 (0.45 to 7.55)**	**0,0073**
ABPM - average daytime BP (mean SD) -mmHg-	**95.5 (9.03)**	**96.2 (13.3)**	**98.0 (11.8)**	**0,249**
Mean difference (95% CI)	**0 (Ref)**	**0.61 (-3.44 to 4.65)**	**2.45 (-2.1 to 7)**	**0,2214**
Adjusted mean difference (95% CI)	**0 (Ref)**	**2.66 (-1.34 to 6.65)**	**5.06 (0.45 to 9.66)**	**0,0422**
ABPM - daytime systolic BP (mean SD) -mmHg-	131 (12.6)	132 (15.2)	135 (17.2)	0,104
Mean difference (95% CI)	0 (Ref)	1.52 (-3.48 to 6.52)	4.42 (-1.22 to 10.05)	0,0964
Adjusted mean difference (95% CI)	0 (Ref)	2.13 (-3.01 to 7.26)	5.51 (-0.43 to 11.45)	0,0565
ABPM - daytime diastolic BP (mean SD) -mmHg-	**77.2 (9.83)**	**75.1 (10.7)**	**78.0 (11.6)**	**0,472**
Mean difference (95% CI)	**0 (Ref)**	**-2.12 (-5.65 to 1.41)**	**0.78 (-3.19 to 4.76)**	**0,2064**
Adjusted mean difference (95% CI)	**0 (Ref)**	**0.67 (-2.53 to 3.86)**	**3.57 (-0.13 to 7.27)**	**0,0233**
ABPM - average nighttime BP (mean SD) -mmHg-	86.9 (11.6)	87.7 (12.2)	**91.6 (11.7)**	**0,021**
Mean difference (95% CI)	0 (Ref)	0.82 (-3.12 to 4.76)	**4.73 (0.3 to 9.15)**	**0,0115**
Adjusted mean difference (95% CI)	0 (Ref)	1.54 (-2.49 to 5.57)	**5.72 (1.08 to 10.35)**	**0,0061**
ABPM - nighttime systolic BP (mean SD) -mmHg-	**121 (14.6)**	**124 (17.8)**	**127 (15.6)**	**0,05**
Mean difference (95% CI)	**0 (Ref)**	**2.99 (-2.48 to 8.46)**	**6.07 (-0.11 to 12.24)**	**0,0613**
Adjusted mean difference (95% CI)	**0 (Ref)**	**2.51 (-3.11 to 8.12)**	**5.89 (-0.62 to 12.39)**	**0,0708**
ABPM - nighttime diastolic BP (mean SD) -mmHg-	68.8 (9.65)	66.9 (10.6)	71.2 (10.8)	0,098
Mean difference (95% CI)	0 (Ref)	-1.85 (-5.28 to 1.58)	**2.43 (-1.43 to 6.3)**	**0,0214**
Adjusted mean difference (95% CI)	0 (Ref)	0.05 (-3.27 to 3.36)	**4.12 (0.29 to 7.95)**	**0,0052**

The adjusted models included the confounding factors age, sex and body mass index. Statistically significant p values (<0.05) are shown in bold. Abbreviations: ABPM = Ambulatory blood pressure monitoring; OSA=Obstructive sleep apnea. Note: Prevalence Non OSA (AHI<5), Mild-Moderate OSA (5≥AHI<30), Severe OSA(30≥AHI).

Table 3. Sleep characteristics in groups with controlled and uncontrolled BP groups

	Controlled (n=132)	Uncontrolled (n=152)	p value
Apnea-Hypopnea Index (median [p_{25};p_{75}]) -events/h-	17.6 [8.35;28.4]	15.4 [7.55;33.3]	0.964
Mean difference (95% CI)	0 (Ref)	0.78 (-3.91 to 5.47)	0.7429
Adjusted mean difference (95% CI)	0 (Ref)	2.2 (-2.28 to 6.69)	0.3344
Hypopnea Index (median [p_{25};p_{75}]) -events/h-	**11.7 [4.95;20.2]**	**9.30 [4.35;21.9]**	**0.451**
Mean difference (95% CI)	**0 (Ref)**	**-1.28 (-6.29 to 3.72)**	**0.6144**
Adjusted mean difference (95% CI)	**0 (Ref)**	**-1.68 (-6.63 to 3.28)**	**0.5058**
Apnea Index (median [p_{25};p_{75}]) -events/h-	5.60 [1.60;14.7]	5.15 [1.10;14.8]	0.82
Mean difference (95% CI)	0 (Ref)	0.72 (-3.43 to 4.86)	0.7341
Adjusted mean difference (95% CI)	0 (Ref)	1.48 (-2.64 to 5.59)	0.4808
ODI 4% (median [p_{25};p_{75}]) -%-	**13.3 [5.90;22.4]**	**11.2 [5.80;24.7]**	**0.585**
Mean difference (95% CI)	**0 (Ref)**	**-0.07 (-4.17 to 4.04)**	**0.9751**
Adjusted mean difference (95% CI)	**0 (Ref)**	**1.32 (-2.55 to 5.2)**	**0.5013**
Obstructive + mixed events (median [p_{25};p_{75}]) -%-	89.0 [22.0;100]	81.5 [19.2;100]	0.282
Mean difference (95% CI)	0 (Ref)	-3.33 (-12.65 to 5.99)	0.4822
Adjusted mean difference (95% CI)	0 (Ref)	0.61 (-8.24 to 9.46)	0.8922
CT90 (median [p_{25};p_{75}]) -%-	**14.5 [4.00;40.1]**	**6.60 [1.95;24.8]**	**0.024**
Mean difference (95% CI)	**0 (Ref)**	**-5.03 (-10.59 to 0.53)**	**0.0759**
Adjusted mean difference (95% CI)	**0 (Ref)**	**-2.64 (-7.87 to 2.59)**	**0.3217**
Mean. O_2 saturation (median [p_{25};p_{75}]) -%-	91.2 [90.0;93.0]	92.0 [90.4;93.1]	0.042
Mean difference (95% CI)	0 (Ref)	0.49 (-0.05 to 1.04)	0.0765
Adjusted mean difference (95% CI)	0 (Ref)	0.23 (-0.27 to 0.74)	0.3657
Min. O_2 saturation (median [p_{25};p_{75}]) -%-	**80.0 [73.0;84.0]**	**81.0 [74.8;85.0]**	**0.208**
Mean difference (95% CI)	**0 (Ref)**	**1.33 (-0.9 to 3.56)**	**0.241**
Adjusted mean difference (95% CI)	**0 (Ref)**	**0.75 (-1.45 to 2.94)**	**0.5045**
Total sleep time[§]	338 [278;368]	316 [256;381]	0.868
Mean difference (95% CI)	0 (Ref)	20.82 (-61.43 to 103.08)	0.6093
Adjusted mean difference (95% CI)	0 (Ref)	13.42 (-75.86 to 102.7)	0.7604
Sleep efficiency[§]	**80.5 [66.3;85.7]**	**71.1 [59.7;84.0]**	**0.225**
Mean difference (95% CI)	**0 (Ref)**	**-6.7 (-16.71 to 3.32)**	**0.1816**
Adjusted mean difference (95% CI)	**0 (Ref)**	**-7.48 (-18.05 to 3.08)**	**0.1569**

The adjusted models included the confounding factors age, sex and body mass index. Statistically significant p values (<0.05) are shown in bold. Abbreviatons: ODI= Oxygen desaturation index; CT90 = Percentage of time with a oxigen saturation lower than 90%. [§] patients diagnosed by polysomnography (n = 34).The apnea index is the total number of apneas per hour (including obstructive, mixed and central apneas). Obstructive+mixed events: percentage corresponding to obstructive and mixed apneas of the total number of apneas.

SUPPLEMENTAL MATERIAL

e-Table 1: Characteristics, ABPM parameters and OSA parameters in participants with controlled and uncontrolled RH.

	Controlled (n=132)	Uncontrolled (n=152)	p value
Sociodemographic and anthropometric characteristics			
Age (years) -Me[p25;p75]-	65.0 [59.0;69.0]	64.0 [56.8;69.0]	0,201
Sex (female) -n (%)-	36 (27.3%)	44 (28.9%)	0,857
BMI (kg/m2) -Me[p25;p75]-	31.1 [28.6;34.3]	31.1 [27.4;33.8]	0,357
ABPM parameters			
Average 24h BP (mmHg) -Me[p25;p75]-	87.0 [83.0;90.0]	100 [96.0;106]	<0.001
Average daytime BP (mmHg) -Me[p25;p75]-	89.0 [85.0;92.0]	102 [97.0;109]	<0.001
Average nighttime BP (mmHg) -Me[p25;p75]-	81.0 [77.0;86.2]	94.0 [88.0;102]	<0.001
Obstructive sleep apnea			
AHI ≥ 5 (events/hour)	108 (81.8%)	129 (84.9%)	0,591
Crude odds ratio (95% CI)	1 (Ref)	1.25 (0.67 to 2.32)	0,4872
Adjusted odds ratio (95% CI)	1 (Ref)	1.17 (0.71 to 1.94)	0,5306
AHI ≥ 15 (events/hour)	69 (52.3%)	78 (51.3%)	0,915
Crude odds ratio (95% CI)	1 (Ref)	0.95 (0.6 to 1.5)	0,826
Adjusted odds ratio (95% CI)	1 (Ref)	1.17 (0.71 to 1.94)	0,5306
AHI ≥ 30 (events/hour)	30 (22.7%)	44 (28.9%)	0,316
Crude odds ratio (95% CI)	1 (Ref)	1.37 (0.81 to 2.33)	0,2386
Adjusted odds ratio (95% CI)	1 (Ref)	1.69 (0.97 to 2.99)	0,4797

Abbreviations: BMI= body mass index; AHI= apnea/hypopnea index; BP = blood pressure

Note: Controlled blood pressure was defined as the following values on the average 24-h ABPM: systolic <130 mmHg and diastolic < 80 mmHg.