ORIGINAL ARTICLE

Association Between Plasma Aldosterone and Sleep Apneas in Arterial Hypertension

Asociación entre aldosterona plasmática y apneas del sueño en hipertensión arterial

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ABSTRACT

Background: Hypertension and obstructive sleep apneas and hypopneas are highly prevalent, frequently associated diseases, mainly in patients with resistant hypertension. In these patients, aldosterone levels correlate with obstructive sleep apnea severity and its blockade reduces seriousness. It has been reported that obstructive sleep apnea could intensify aldosterone secretion and this could be one of the mechanisms that increase blood pressure. However, there is little evidence demonstrating its relationship with the severity of obstructive sleep apnea in the population with suspected hypertension.
Objective: The aim of this study was to establish the association between plasma aldosterone and obstructive sleep apnea in patients with suspected hypertension without pharmacological treatment.
Methods: This was a prospective, descriptive observational study. Hypertension was diagnosed by ambulatory monitoring of blood pressure. The clinical suspicion of obstructive sleep apnea was evaluated by self-administered home respiratory polygraphy and severity was defined according to the apnea-hypopnea index per registry hour. Plasma aldosterone was assessed from a morning blood sample in the same evaluation session.
Results: A total of 109 patients were included in the study. Baseline aldosterone was higher in patients with obstructive sleep apnea independently of whether they were or not hypertensive ($p < 0.05$). A stepwise aldosterone increase was found as obstructive sleep apnea was more severe in normotensive patients ($p < 0.05$), while in the hypertensive group, the same pattern was found, but without significant differences.
Conclusion: A proportional increase in aldosterone, blood glucose and cardiovascular risk was found with increased sleep apnea severity.

Key words: Hypertension - Aldosterone - Sleep Apnea Syndromes

RESUMEN

Introducción: La hipertensión arterial y las apneas e hipopneas obstructivas del sueño son patologías de alta prevalencia frecuentemente relacionadas, fundamentalmente en pacientes con hipertensión arterial resistente. En los pacientes con esta afección, los niveles de aldosterona se correlacionan con la gravedad de la apnea obstructiva del sueño y su bloqueo reduce la gravedad. Se ha afirmado que la apnea obstructiva del sueño podría aumentar la secreción de esta hormona y que este podría llegar a ser uno de los mecanismos involucrados en el aumento de la presión arterial. Sin embargo, poca evidencia demuestra su relación con la gravedad de la apnea obstructiva del sueño en la población con sospecha de hipertensión arterial.
Objetivo: determinar la asociación entre aldosterona plasmática y la apnea obstructiva del sueño en pacientes con sospecha de hipertensión arterial sin tratamiento farmacológico.
Material y método: Se diseñó un estudio prospectivo, observacional y descriptivo. El diagnóstico de hipertensión arterial se realizó mediante monitoreo ambulatorio de la presión arterial. La sospecha clínica de apnea obstructiva del sueño fue evaluada mediante poligrafía respiratoria domiciliaria autoadministrada y se definió gravedad según el índice de apneas e hipopneas por hora de registro. La medición de aldosterona plasmática se realizó en una extracción matinal en la misma evaluación.
Resultados: Se incluyeron 109 pacientes. La apnea obstructiva del sueño presentó mayor nivel basal de aldosterona independientemente que fuesen o no hipertensos ($p < 0,05$) y existió un incremento escalonado a medida que aumentaba la gravedad de la apnea obstructiva del sueño en pacientes normotensos ($p < 0,05$), mientras que, en el grupo de hipertensión arterial, se halló el mismo patrón, pero sin diferencias significativas.
Conclusión: Se pudo observar un aumento proporcional de los valores de aldosterona, glucemia y riesgo cardiovascular a medida que se incrementaba la gravedad de la apnea del sueño.

Palabras clave: Hipertensión - Aldosterona - Síndromes de la apnea del sueño

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Abbreviations

ABPM	Ambulatory blood pressure monitoring	**CPAP**	Continuous positive airway pressure
AHI	Apnea-hypopnea index	**HT**	Hypertension
BP	Blood pressure	**OSA**	Obstructive sleep apneas and hypopneas

INTRODUCTION

Hypertension (HTN) and obstructive sleep apnea-hypopnea (OSA) are highly prevalent, frequently associated diseases, mainly in patients with resistant HTN. (1-3)

Hypertension affects 36% of the adult population and its lack of control or treatment leads to cardiovascular disease, heart failure, acute myocardial infarction, kidney failure and stroke after years of exposure. (4)

Obstructive sleep apnea-hypopnea is an emerging health issue, affecting more than 15% of men and more than 10% women in the total adult population, (5) and it is associated with morbidity and mortality attributable to traffic, labor and domestic accidents and the development of cardiovascular and cerebrovascular complications. (6, 7)

It has been reported that patients with sleep apneas have hypercapnic and hypoxemic episodes secondary to the development of respiratory events. These phenomena generate sympathetic nervous system activation with subsequent increased release of serum catecholamines and, consequently, heart rate and blood pressure (BP) elevation by a mechanism of reflex vasoconstriction. (8) Other triggers are the proinflammatory effect, increased oxidative stress and increased vascular stiffness. (9)

Its severity assessed through the apnea-hypopnea index (AHI) is accompanied by changes in cardiovascular parameters, mainly BP and heart rate oscillations. (10-12) One of the cardiovascular regulatory systems affected by OSA is the baroreflex mechanism. This would alter chemoreflex activation secondary to intermittent hypoxia, contributing to acute and chronic BP increase. (13-15) It has been observed that only two weeks of nocturnal intermittent hypoxemia in patients without associated disease could increase systolic and diastolic BP by 8 mmHg and 5 mmHg, respectively. (15, 16)

Data from our country describe that approximately 50% of individuals with OSA are hypertensive (17, 18) and that 44% of hypertensive patients referred to specialized cardiological consultation had moderate to severe sleep apneas and were candidates for treatment with continuous positive airway pressure (CPAP). (19)

There is a dose-effect relationship between HTN and OSA severity, and for each event/h of AHI increase, there is the possibility of a 1% rise in the development of HTN. (16, 20-22)

Occult HTN is underestimated in patients with OSA, and this is often revealed by 24-hour ambulatory blood pressure monitoring (ABPM) in 42% to 80% of cases. (16, 22-24)

Numerous studies demonstrate that subjects with moderate-severe OSA (AHI >15 events/h) have more probability of being hypertensive than subjects of similar age and body weight, but without OSA. (16) In the Wisconsin Sleep Cohort Study, normotensive subjects with moderate-severe OSA tripled the risk of developing HTN during a 4-year follow-up compared with patients without OSA. (16) In addition, it has been observed that the greater the OSA severity, the higher the number and dose of anti-hypertensive drugs required to achieve the same BP control than in patients with less severe OSA. (16)

Continuous positive airway pressure treatment has shown consistent though modest antihypertensive benefit, with wide difference in response from one patient to another, and with greater benefit in severe OSA, higher BP levels and device use adherence. (16, 20) Although improvement in BP values varies in the range of -2 mmHg, small interventional trials suggest that chronic CPAP use reduces the sustained activity of the sympathetic system and improves the baroreflex function and proinflammatory state, thus decreasing cardiovascular risk. (13, 16, 20)

Conversely, in patients with resistant HTN, aldosterone levels correlate with OSA severity and its blockade reduces seriousness. (16) Obstructive sleep apnea-hypopnea could increase this hormone and this could be one of the mechanisms involved in enhanced BP. (25) In a prospective study including 114 patients with resistant HTN, those with elevated risk of OSA reported greater 24-hour excretion of urinary aldosterone using the Berlin questionnaire. (20)

Two possibilities have been posed: that OSA stimulates aldosterone release or that excess aldosterone worsens preexistent OSA, although lack of a constant CPAP effect on aldosterone levels in several studies seems a contradictory argument. (20) However, clinical data document the opposite effect, i.e. excess aldosterone worsens OSA severity, since spironolactone (aldosterone antagonist) decreases moderate-severe OSA seriousness. (21, 27, 28) In this sense, some authors have proposed the caudo-rostral fluid redistribution phenomenon as a mechanism linking the genesis of sleep apnea in hypertensive patients through the increase in the collapsibility of the upper airway. (26)

Based on the above, there is a relationship between plasma aldosterone and OSA, and most scientific evidence has been obtained from populations with resistant HTN. Therefore, the objective of the present study was to assess aldosterone levels in patients with suspected HTN and risk of OSA referred to a specialized

center before receiving pharmacological treatment and to establish its relationship with OSA severity.

METHODS

This was a prospective, observational and descriptive study in adult patients with suspected HTN and untreated OSA at the time of consultation.

The following criteria had to be fulfilled for inclusion in the study: patients older than 18 years evaluated at the Arterial Hypertension Center of Hospital Británico of Buenos Aires between January and October 2017 with suspected HTN untreated at the time of inclusion.

A 24-hour ABPM registry was systematically performed to confirm the diagnosis of HTN as well as a nocturnal home respiratory polygraphy registry.

Routine blood tests included plasma aldosterone assessment, plasma renin activity and calculation of the aldosterone/renin ratio.

Aldosterone and renin were measured from a fasting baseline morning blood sample after supine rest for at least 30 minutes. Blood samples were then processed in situ by radioimmunoassay.

Exclusion criteria were prior known diagnosis of primary hyperaldosteronism, antihypertensive pharmacological treatment, contraindication to perform ABPM, need for urgent pharmacological treatment, uncontrolled diabetes, known moderate to severe chronic obstructive pulmonary disease, prior treatment with CPAP, acute or chronic heart failure, moderate to severe kidney failure, impossibility or intolerance to perform a respiratory polygraphy, uncontrolled thyroid disease and complete suppression of plasma renin activity.

Office BP was assessed following national and international guidelines (29, 30) with an automatic arm blood pressure monitor (OMRON 7220). Three measurement were taken separated by 2 minutes each, discarding the first one and considering the average between the last two.

A Spacelabs Ultralite device (model 90217, SpaceLabs, Redmond, WA) was used for ABPM. The device was programmed to assess BP every 15 minutes during daytime (8:00 a.m. to 11:00 p.m.) and every 30 minutes during nighttime (11:00 p.m. to 8:00 a.m.), and then adjusted to the patient´s diary. Normotension was defined as daytime and nighttime BP ≤135/85 mmHg and 120/70 mmHg, respectively. Ambulatory blood pressure monitoring and respiratory polygraphy were performed on successive nights.

Respiratory polygraphy was done with a 5-channel Apnea Link Plus™ (ResMed, Australia) device with three basic signals: pulse oximetry, airflow by nasal cannula and thoracic effort (level III devices of the American Academy of Sleep Medicine). (31) Only registries with a total recording time in the manual analysis >240 min (>4 h) were accepted as valid. Apnea was defined as airway flow reduction above 80% from baseline for ≥10 s and hypopneas were considered as 50% airway flow reduction for ≥10 s associated with desaturations ≥3%. The AHI was calculated as number of apneas/hypopneas per hour of valid evaluation and is expressed as events per hour (ev/h). (32) Patients were classified as: Non-OSA (AHI <5 ev/h), mild OSA (AHI ≥5.1 and <15 ev/h) and moderate-severe OSA (AHI ≥15 ev/h).

According to study results, patients were classified in 6 categories:

Normotensive without OSA (GI Non-HTN) with AHI <5 ev/h.

Normotensive with mild OSA (GII Non-HTN) with AHI between 5.1 and 15 ev/h.

Normotensive with moderate-severe OSA (GIII Non-HTN) with AHI >15 ev/h-

Hypertensive without OSA (GI HTN) with AHI <5 ev/h.

Hypertensive with mild OSA (GII HTN) with AHI between 5.1 and 15 ev/h.

Hypertensive with moderate-severe OSA (GIII HTN) with AHI >15 ev/h-

Statistical analysis

Results were expressed as percentage for categorical variables or mean and standard deviation for numerical variables. Variables with normal distribution were expressed as mean and standard deviation, and those with non-normal distribution as mean and percentile (25%-75%). Fisher, Kruskal Wallis and Dunn's multiple comparisons tests were used to compare differences. The p value of statistical significance was calculated once the predictive variables were obtained. A p value <0.05 was considered as statistically significant. Graph Pad Prism 7.04™ software was used for the statistical analysis.

Ethical considerations

The study was approved by the institutional Review Board of Hospital Británico de Buenos Aires following the Declaration of Helsinki norms and their subsequent revisions.

RESULTS

A total of 109 patients were included with the following distribution: GI Non-HTN (16 patients), G2 Non-HTN (15 patients), GIII Non-HTN (9 patients), GI HTN (26 patients), GII HTN (19 patients) and GIII HTN (24 patients).

GI Non-HTN patients presented with lower waist and neck circumference than GII and GIII Non-HTN patients ($p<0.05$) and no significant differences were observed between groups for age and body mass index (BMI) (Table 1).

In the group of patients with HTN, there was greater prevalence of smokers, diabetics (treated with oral hypoglycemic drugs and/or insulin) and patients with dyslipidemia (treated with oral lipid-lowering agents, and/or with total cholesterol, LDL or triglycerides above the normal reference value). There were also significant differences in age, waist circumference, neck circumference and BMI ($p<0.05$), which were greater in the group with moderate-severe OSA (Table 1B).

Overall cardiovascular risk assessed using the ACC/AHA calculator showed that risk was higher in GII and GIII Non-HTN compared with GI Non-HTN patients, same as in GI HTN vs. GII and GIII HTN patients (Tables 1A and B), though this increase was not statistically significant.

Significant daytime systolic BP differences were found between GI and GIII HTN patients, with increased ABPM in AHI >15 ev/h (Table 2).

Blood test results showed a stepwise increase in uric acid and lipid levels in patients without HTN, which were statistically significant depending on OSA severity by AHI. The same pattern was observed in

hypertensive patients, but the difference was not significant. Fasting baseline blood sugar levels were higher in HTN than in Non-HTN patients, with a stepwise increase ($p<0.05$, Table 3).

Figure 1 shows that OSA patients presented a progressive (albeit not significant) aldosterone increase, with higher morning baseline plasma levels, regardless of whether patients were or not hypertensive. Additionally, we found a stepwise and proportional increase of aldosterone in the group of normotensive patients as OSA severity by AHI increases, ($p<0.05$). This pattern was not observed in the group of patients with HTN, in whom plasma aldosterone levels showed a slightly increasing trend according to OSA severity, but without statistically significant differences. (Figure 2).

Renin levels and the aldosterone/renin ratio were assessed to rule out patients with primary hyperaldosteronism (Table 3). Renin values were not significantly different between groups, while the aldosterone/renin ratio evidenced a gradual and growing increase between groups, but without significant differences.

Non HTN	GI Non-HTN (n=16)	GII Non-HTN (n=15)	GIII Non-HTN (n=9)
Men (%)	31	33.3	77.7
Age (years)	50.9 ± 12.4	48.5 ± 15.8	57.3 ± 14.7
Waist circumference (cm)	89.7 ± 12	99.7 ± 17.3	108.6 ± 14.4 *
Neck circumference (cm)	35.8 ± 3.1	39.6 ± 4.4	40.8 ± 3.8 **
BMI (kg/m2)	27.6 ± 5.5	32.4 ± 5.8	32.4 ± 7.6
Smoking (%)	6.2%, n: 1	20%, n: 3	11.1%, n:1
Diabetes (%)	6.2%, n: 1	6.6%, n: 1	11.1%, n:1
Dyslipidemia (%)	31.2%, n: 5	60%, n: 9	100%, n: 9
ACC/AHA score	4.5	7	8.6

* p <0.05 for G1 Non-HTN vs. GIII Non-HTN ** p <0.05 for GI Non-HTN vs. GII and GIII Non-HTN. BMI: Body mass index. ACC/AHA score: Risk of cardiovascular events at 10 years according to the American College of Cardiology/American Heart Association calculator.

Table 1. A. Non-hypertensive population variables.

HTN	GI HTN (n=26)	GII HTN (n=19)	GIII HTN (n=24)
Men (%)	42	68.4	66.6
Age (years)	44.4 ± 12.5	49.3 ± 12.61	56 ± 9.6 *
Waist circumference (cm)	89.4 ± 13.5	105.1 ± 9.9	105.5 ± 13.3 **
Neck circumference (cm)	36.9 ± 4.4	41.6 ± 3.2	41.4 ± 3.5 **
BMI (kg/m2)	27.6 ± 6.7	32.2 ± 5.8	32.9 ± 7.3 **
Smoking (%)	23.1%, n: 6	52.6%, n: 10	41.6%, n: 10
Diabetes (%)	3.8%, n: 1	36.8%, n: 7	29.2%, n: 7
Dyslipidemia (%)	19.2%, n: 5	44.4%, n: 8	33.3%, n: 8
ACC/AHA score	4.9	10	10.2

* p <0.05 for GI HTN vs. GIII HTN ** p <0.05 for GI HTN vs. GII HTN and GIII HTN
ACC/AHA score: Risk of cardiovascular events at 10 years according to the American College of Cardiology/American Heart Association calculator. BMI: Body mass index.

Table 1. B. Hypertensive population variables.

Table 2. Office blood pressure and 24-hour ambulatory blood pressure monitoring values

	Without hypertension			Hypertension		
	GI Non-HTN (n=16)	GII Non-HTN (n=15)	GIII Non-HTN (n=9)	GI HTN (n=26)	GII HTN (n=19)	GIII HTN (n=24)
Office systolic BP	122 ± 14	122 ± 14	122 ± 14	122 ± 14	122 ± 14	122 ± 14
Office diastolic BP	80 ± 7	80 ± 7	80 ± 7	80 ± 7	80 ± 7	80 ± 7
Daytime systolic ABPM	118 ± 7	118 ± 7	118 ± 7	118 ± 7	118 ± 7	118 ± 7
Daytime diastolic ABPM	74 ± 6	74 ± 6	74 ± 6	74 ± 6	74 ± 6	74 ± 6
Nighttime systolic ABPM	106 ± 9	106 ± 9	106 ± 9	106 ± 9	106 ± 9	106 ± 9
Nighttime diastolic ABPM	64 ± 5	64 ± 5	64 ± 5	64 ± 5	64 ± 5	64 ± 5

BP: Blood pressure. ABPM: Ambulatory blood pressure monitoring

Table 3. Laboratory data

Categories	Non-HTN			HTN		
Groups	GI Non-HTN (n=16)	GII Non-HTN (n=15)	GIII Non-HTN (n=9)	GI HTN (n=26)	GII HTN (n=19)	GIII HTN (n=24)
Uric acid (mg/dL)	5 ± 1*	5.6 ± 1	6 ± 1*	5 ± 1	5.6 ± 1.2	5.6 ± 1.2
Glucose (mg/dL)	89 ± 18	93 ± 11	95.5 ± 14	91 ± 8.5**	100.6 ± 30.2**	101 ± 30.5**
Hb1Ac (%)	5.5 ± 0.3	5.5 ± 0.6	5.7 ± 0.66	5.4 ± 0.25	5.9 ± 1.6	5.9 ± 1.6
Triglycerides (mg/dL)	91 ± 33	129.5 ± 55	127.2 ± 51	140 ± 106	142 ± 105	151.8 ± 73.6
Total cholesterol (mg/dL)	173 ± 30**	201 ± 35**	201 ± 30**	190 ± 42	194 ± 38	196 ± 38
Creatinine (mg/dL)	0.8 ± 0.1	0.8 ± 0.1	0.85 ± 0.12	0.8 ± 0.1	0.9 ± 0.13	0.9 ± 0.12
Aldosterone (pg/mL)	120 ± 88	132.4 ± 98.3	138.4 ± 98.4	128 ± 61.2	130 ± 76	133 ± 76
Renin (ngA1/mL/h)	1.9 ± 0.9	1.7 ± 1.3	1.4 ± 0.5	2.2 ± 1.5	1.8 ± 1.0	1.4 ± 0.8
Aldosterone/renin ratio	8.7 ± 5.7	9 ± 5.1	12.7 ± 7.9	2.3 ±1.4	10.3 ± 7	11 ± 6.5

* p <0.05 between two groups and ** p <0.05 for GI Non-HTN vs. GII and GIII.

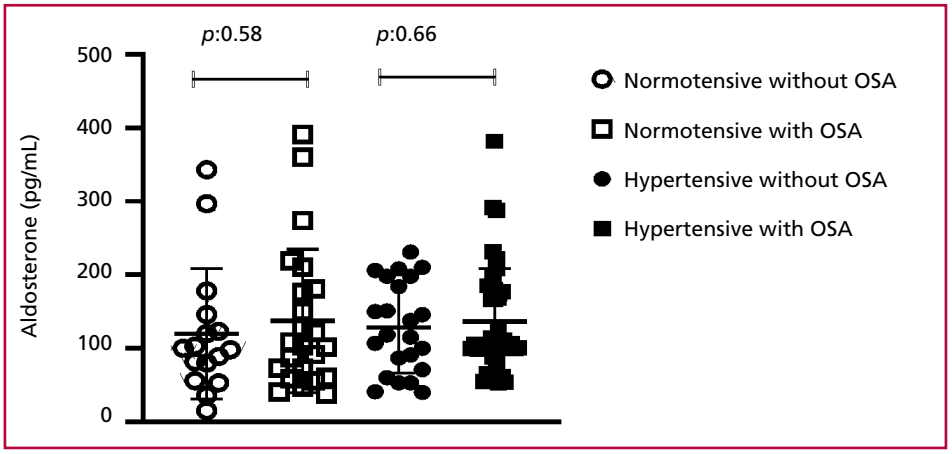

Fig. 1. Mean plasma aldosterone values related with HTN diagnosis and AHI >5 ev/h in respiratory poligraphy. Mean baseline aldosterone was higher in hypertensive patients (139.1 ± 88.6 vs. 127.4 ± 83.3).

OSA: Obstructive sleep apnea

DISCUSSION

There is a relationship between HTN and OSA and both increase morbidity and mortality; it is therefore relevant to understand the interaction between both pathologies.

This study suggests that OSA could be linked to modifications in aldosterone values independently of HTN.

Interestingly, a stepwise increase was observed between OSA and aldosterone values in Non-HTN patients ($p<0.05$), while in the HTN group a growing trend was seen but without statistically significant differences. This could be due to two possible reasons: the first might be statistical, since, to obtain statistical significance, the sample size with these values would be 266 patients with a zeta power of 1.96, and the second could be that baseline aldosterone values in hypertensive patients would correspond to a different physiopathogenic pathway.

Studies analyzing the role of aldosterone in OSA were generally carried out in patients with severe or resistant HTN, or else, in hypertensive populations treated with drugs (even anti-aldosterone agents) which could have affected the interpretation. (16, 20)

The results of independent cardiovascular risk factors, as waist circumference, neck circumference, BMI and laboratory glycemic and lipid profiles are possibly reflected as a whole in the ACC/AHA score, leading us to the conclusion that hypertensive patients with OSA present higher cardiovascular risk. (19, 33)

A discrete elevation in office BP as in daytime and nighttime ABPM values was observed in hypertensive patients, as AHI-assessed severity increased. Blood pressure and ABPM values consistent with diagnostic criteria of HTN were associated with higher aldosterone levels than those found in the Non-HTN group.

The increase pattern of plasma aldosterone showed a proportional and stepwise significant trend in normotensive patients dependent on OSA severity. Thus, we found that aldosterone increases with a gradual slope in the normotensive group, which is attributable to a dose-response biological phenomenon, possibly as

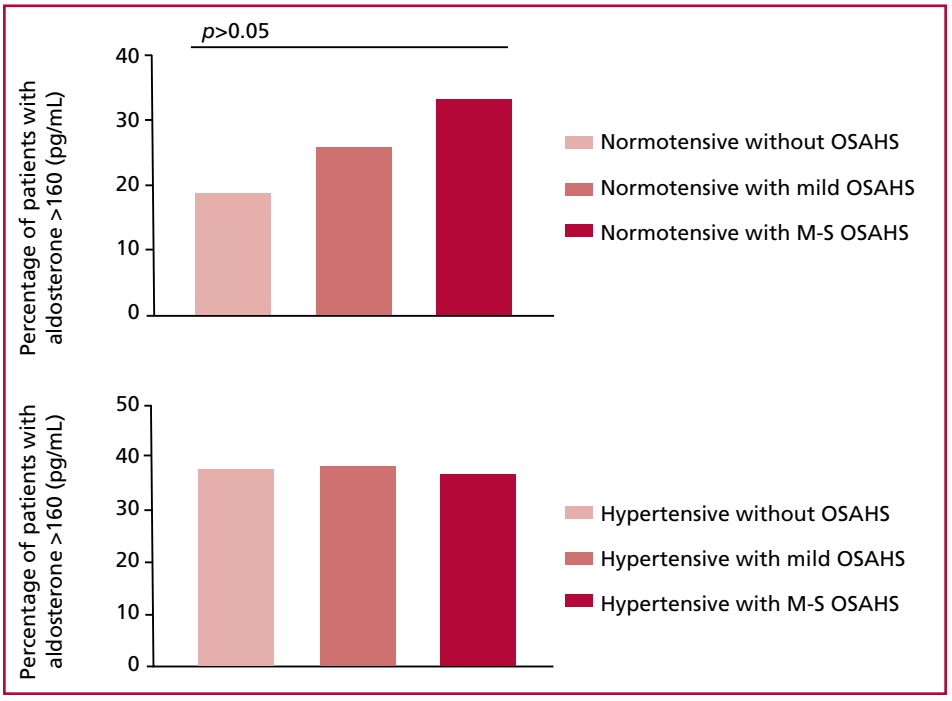

Fig. 2. Distribution according to plasma aldosterone values >160 pg/dL (reference value).

OSAHS: Obstructive sleep apnea and hypopnea syndrome. M-S: Moderate-severe.

a consequence of increased AHI and the degree of nocturnal hypoxemia.

In our population, the percentage of patients with baseline aldosterone >160 ng/ml was 35% with AHI >15 ev/h versus 40% in the HTN group. In agreement with the Birmingham group hypothesis, it is possible that in OSA patients there is an important role of aldosterone and that hydrosaline retention, with fluid displacement from the tissues to the neck, is associated with AHI severity. (20) We did not perform physiological measurements of fluid displacement in these patients and this represents, to a certain extent, a limitation of the study.

Additionally, the strengths of the present analysis lie in the definition of HTN using a systematic ABPM reading together with a standardized technique for sleep studies by experts in sleep medicine, (17, 19) and to the fact that we included untreated (naïve) patients at the time of assessment, of whom there is scarce information. Studies with a larger number of subjects are necessary to confirm our findings, which must be seen as generators of hypotheses. The small sample size may cause a significant beta error which should be corrected with the continuation of this and other studies along the same line of research.

Finally, our results show a proportional increase of aldosterone, blood glucose and cardiovascular risk values as the severity of sleep apnea increases.

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Conflicts of interest
None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material).

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