Archivos de Bronconeumología 58 (2022) 369–371

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

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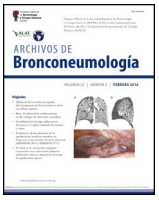

Scientific letter

Is There an Association Between Nocturia and Nighttime Hypertension in Patients With Moderate to Severe Sleep Apnea?☆

¿Existe una asociación entre nicturia e hipertensión nocturna en pacientes con apnea del sueño moderada-grave?

To the Director,

An elevated blood pressure (BP) and the lack of BP physiological decrease during sleep (non-dipping) are demonstrated cardiovascular risk factors.[1,2] Nocturia is a multifactorial, highly prevalent symptom in the general population.[3,4] Nocturia and nighttime hypertension are common in patients with obstructive sleep apnea (OSA) and share several physiopathological pathways.[5–7] An association between both conditions has been described in the general population and in OSA[8,9] but, so far, studies have not properly assessed OSA and hypertension.[10,11] We hypothesized that there is an association between nocturia and nocturnal hypertension/non-dipping status in non-treated moderate-severe OSA and that the presence of nocturia could represent an OSA phenotype at increased cardiovascular risk. Our aim was to assess whether nocturia is a predictive factor of nocturnal hypertension/non-dipping status in this population.

Subjects underwent an overnight home sleep study with a portable device (Alice One (Philips Respironics) with manual scoring.[12] Subjects with an apnea-hypopnea index (AHI) > 20 events/hour were offered to participate in the study and gave informed consent. In addition to the AHI, 3% and 4% oxygen desaturation index (ODI3% and ODI4%) and cumulative time at SaO_2 < 90% (CT90%) were recorded for analysis. Anthropometric variables (age, gender, body mass index (BMI), neck circumference), smoking status (packs/years), alcohol consumption (alcohol units/day), active medication and comorbidities (hypertension, diabetes, dyslipidemia, ischemic heart disease, heart failure, arrhythmias, stroke, insomnia, depression, prostatic syndrome) were recorded from clinical interview, clinical examination and medical records. Nocturia was defined as ≥2 voids from going to bed until awakening,[4] in the last 3 nights, obtained by clinical interview. Patients completed the Epworth sleepiness scale[13] and the Spanish version of the Pittsburg sleep quality test.[14] Fasting blood, recent urine samples and 24-h urine volume were collected to measure biochemical measurements: glycemia, HbA1c, total, HDL and LDL cholesterol, creatinine, renin, aldosterone, brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-pro BNP), and antidiuretic hormone (ADH); beta-2-microglobulin, creatinine and albuminuria were quantified in recent urine samples and albuminuria and urine volume were quantified in 24-h urine samples. Lower urinary tract ultrasonography was performed to assess prostatic volume and post-void volume. Ambulatory BP monitoring (ABPM) with a Space Labs 90217 monitor (Space Labs; OSI Systems, Hawthorne, CA, USA) was used to measure 24-h BP and heart rate (set every 20 min during the daytime period (6 AM–10 PM) and every 30 min during the nighttime period (10 PM–6 AM)). The cut-off values for hypertension were mean daytime BP > 130/80 mmHg and/or nighttime BP > 120/70 mmHg. Non-dipping was defined as a ≤10% reduction in BP during the nighttime compared with the daytime period.[15]

Exclusion criteria were renal insufficiency, uncontrolled diabetes (serum glycemia > 180 mg/dL), urinary infection, primary hyperaldosteronism or treatment with aldosterone antagonist drugs, active CPAP treatment, patients evaluated for bariatric surgery and subjects with shift-work or a night-time shift.

The sample size calculation showed that 164 individuals were required to detect a difference equal to or greater than 6 mmHg in nocturnal systolic BP[7] between OSA patients with and without nocturia. A common standard deviation of 13 mmHg[16] and a 10% loss of follow-up were assumed.

Three backward stepwise multivariable logistic regression models were carried out in order to identify variables related to nocturnal hypertension, non-dipping and nocturia. Variables with a P value < 0.2 in the univariate analysis were included as independent variables (except renin and aldosterone which were not included to avoid over-adjusting, assuming their role as hypertension mediating factors). Quantitative independent factors related to the main outcomes were transformed to binary variables using the best predictive cut-off point of each selected. Receiver Operating Characteristic (ROC) curve analysis were used for this approach. The combination of predictors from the final models were used to calculate the probabilities of the outcomes. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the model.[17]

Among 164 consecutive patients evaluated, 142 fulfilled inclusion criteria. Hypertension during 24-h was observed in 61 subjects (43%), during daytime in 51 (35.9%) and during nighttime in 73 (51.4%), without significant differences between those with or without nocturia. A non-dipping pattern was observed in 83 patients (58.5), more prevalent in those with than without nocturia (72% vs 51.1%; P = 0.016).

In patients with nighttime hypertension compared to those without, both AHI and CT90% were significantly higher (47.3 (18.5) vs 41 (18.3); P = 0.043, and 23.6% (23.3) vs 15.2% (17.2); P = 0.040, respectively). Non-dippers, as compared with dippers, showed a significantly higher AHI (47.6 (19.4) vs 39.5 (16.4), respectively; P = 0.026) and a higher, although not significantly, CT90% (21.7% (21.6) vs 16.5% (19.7) respectively; P = 0.078).

☆ This work was performed at Vall d'Hebron University Hospital in Barcelona, Spain.

https://doi.org/10.1016/j.arbres.2021.09.014

Table 1
Anthropometric characteristics, sleep studies, lower urinary tract ultrasound and ABPM findings in moderate-severe OSA patients according to the presence or absence of nocturia.

Variable	Statistic	Total ($N=142$)	Nocturnal voids		P-value
			<2 ($N=92$)	≥2 ($N=50$)	
Male gender	n (%)	113 (79.6%)	77 (83.7%)	36 (72%)	0.099
Age	Mean (SD)	57.5 (9.9)	56.8 (10)	59. (9.7)	0.411
Height (cm)	Mean (SD)	167.9 (8.4)	169.5 (8)	164.8 (8.5)	0.002
Weight (kg)	Mean (SD)	90.8 (16.5)	89.9 (16.7)	92.9 (16.2)	0.351
BMI (kg/m^2)	Mean (SD)	32.3 (6)	31.3 (6)	34.1 (5.6)	0.002
Tobacco: packs/year	Mean (SD)	9.5 (16.5)	11.2 (17.1)	5.9 (14.9)	0.038
Alcohol: alcohol units/day	Mean (SD)	1.2 (4.6)	1.4 (5.6)	0.7 (1.32)	0.464
Number of voids (sleep time)	Mean (SD)	1.3 (1.)	0.6 (0.6)	2.5 (0.65)	<0.001
Abdominal perimeter (cm)	Mean (SD)	112.3 (11.9)	111.1 (11.8)	114.6 (12)	0.174
Neck circumference (cm)	Mean (SD)	42.2 (3.6)	42.5 (3.5)	41.6 (3.8)	0.574
ESS	Mean (SD)	7.2 (4)	7.1 (4.1)	7.5 (3.68)	0.345
Pittsburg	Mean (SD)	7.5 (3.8)	6.9 (3.5)	8.8 (4.1)	0.01
AHI	Mean (SD)	44.2 (18.6)	41.2 (17.7)	50.1 (19.2)	0.007
ODI3%	Mean (SD)	44 (19.1)	40.8 (18.9)	49.9 (18.3)	<0.001
ODI4%	Mean (SD)	33.6 (22.3)	28.4 (19.5)	46.2 (24.3)	0.005
CT90%	Mean (SD)	19.5 (20.9)	16.7 (18.5)	24.9 (24.3)	0.043
Diagnosed Hypertension	n (%)	72 (50.7%)	43 (46.7%)	29 (58%)	0.200
Prostate Hyperplasia ($n=75$)	n (%)	31 (41.3%)	22 (40%)	9 (45%)	0.697
Post void volume cc	Mean (SD)	10.2 (9.1)	9.8 (9.1)	10.9 (9.4)	0.575
Systolic BP 24-h (mmHg)	Mean (SD)	123.4 (13.5)	122.3 (13.9)	125.5 (12.5)	0.134
Diastolic BP 24-h (mmHg)	Mean (SD)	76.5 (8.3)	76.7 (8.8)	76.3 (7.4)	0.478
Systolic BP daytime (mmHg)	Mean (SD)	125.9 (13.6)	125.1 (14)	127.4 (12.9)	0.298
Diastolic BP daytime (mmHg)	Mean (SD)	78.8 (8.4)	79.31 (8.9)	77.9 (7.6)	0.209
Daytime heart rate (bpm)	Mean (SD)	76.4 (10.7)	76 (10.4)	77.3 (11.2)	0.389
Systolic BP nighttime (mmHg)	Mean (SD)	115.5 (14.7)	113.5 (14.9)	119.1 (13.9)	0.025
Diastolic BP nighttime (mmHg)	Mean (SD)	69.5 (8.8)	69.2 (9.4)	69.9 (7.5)	0.590
Nighttime heart rate (bpm)	Mean (SD)	68.1 (10.5)	67.2 (10.1)	69.5 (11.3)	0.241
24-h hypertension	n (%)	61 (43%)	43 (46.7%)	18 (36%)	0.217
Daytime hypertension	n (%)	51 (35.9%)	34 (37%)	17 (34%)	0.726
Nighttime hypertension	n (%)	73 (51.4%)	45 (48.9%)	28 (56%)	0.420
Non-dipping	n (%)	83 (58.5%)	47 (51.1%)	36 (72%)	0.016

ABPM: ambulatory blood pressure monitoring; BMI: body mass index; AHI: apnea hypopnea index; ODI3%: 3% oxygen desaturation index; ODI4%: 4% oxygen desaturation index; CT90%: cumulative time at SaO_2 < 90%; ESS: Epworth sleepiness scale; BP: blood pressure.

Nighttime hypertension and non-dipping were observed in 48.6% and 63.9% of patients with a clinical diagnosis of hypertension and in 54.3% and 52.9% of patients without a diagnosis of hypertension, without significant differences between both groups of patients ($P=0.499$ and $P=0.188$, respectively).

Patients' characteristics, according to the presence of nocturia, are shown in Table 1. Patients with nocturia ($n=50$, 35.2%) had higher BMI (34.2 (5.6) vs 31.3 (5.9) kg/m^2; $P=0.002$), AHI (50.1 (19.2) vs 41.2 (17.7); $P=0.007$), and CT90% (24.9% (24.3) vs 16.7% (18.5); $P=0.043$), lower concentrations of antidiuretic hormone and renin (1.6 (1.5) vs 2.15 (1.6) mg/dL; $P=0.040$ and 1.5 (2.3) vs 3.2 (6.2) ng/mL/h); $P=0.048$, and higher aldosterone values (16.2 (6.5) vs 13.7 (6) ng/dL; $P=0.027$. Subjective sleep quality was worse in those with nocturia. Among 24-h BP parameters, nighttime systolic BP was significantly higher (119.1 (13.9) vs 115.5 (14.7) mmHg; $P=0.025$), and non-dipping was significantly more prevalent (72% vs 51.1%, respectively; $P=0.016$), in patients with nocturia as compared to those without.

Multivariable logistic regression adjusting for factors showing an association in the univariate analyses ($P<0.20$), showed that CT90% and AHI were independent risk factors for nocturnal hypertension and non-dipping (OR 1.02, CI:1–1.04; $P=0.043$) and (OR 1.02 CI: 1–1.05; $P=0.032$), respectively, but nocturia was not. The best cut-off points (ROC curve) were CT90% ≥ 35% for nocturnal hypertension, and AHI ≥ 45 for non-dipping. Nocturia increased the probability of nocturnal hypertension from 75% to 79% if CT90% ≥ 35, and of non-dipping from 64% to 78%, if AHI ≥ 45 (Tables 2A and 2B). The AHI was the only variable independently associated with nocturia (OR 1.02, 95% CI 1.01–1.05), $P=0.03$).

A few previous studies[10,11] found an independent association of nocturia with hypertension, in large populations, but without assessing OSA and hypertension using both a sleep study and ABPM. Our sample was composed of moderate-severe OSA patients, who were thoroughly assessed by sleep studies, ABPM, and a lower urinary tract ultrasound, so that we were able to control for a number of possible confounder variables; in addition, we provide information on biochemical assessment of natriuretic hormones and peptides. Our study has several limitations such as the small sample size and the subjectivity in the assessment of nocturia.

Table 2
A. Probability of nocturnal hypertension using predictors from the multivariable logistic regression model (Predictors from the model could be used to calculate the probability of nocturnal hypertension by the following formula: $\text{Exp}(\beta)/(1+\text{Exp}(\beta))$, where $\beta = -0.235 + 0.186$ (in case of nocturia (nighttime voids ≥2)) + 1.355 (in case of CT90% ≥ 35).

Risk factor	Probability (%)
None	44%
Nocturia	49%
CT90% ≥ 35	75%
Nocturia + CT90% ≥ 35	79%

B. Probability of non-dipping using predictors from the multivariable logistic regression model (Predictors from the model could be used to calculate the probability of non-dipper by the following formula: $\text{Exp}(\beta)/(1+\text{Exp}(\beta))$, where $\beta = -0.287 + 0.702$ (in case of nocturia (nighttime voids ≥ 2)) + 0.849 (in case of AHI ≥ 45).

Risk factor	Probability (%)
None	43%
Nocturia	60%
AHI ≥ 45	64%
Nocturia + AHI ≥ 45	78%

AHI: apnea hypopnea index; CT90%: cumulative time at SaO_2 < 90%.

In summary, nighttime hypertension and non-dipping were frequent in our series of moderate-severe OSA, in both patients with treated or unknown hypertension. The use of ABPM in this OSA population could identify patients at increased cardiovascular risk. When added to CT90% and AHI, nocturia slightly increased the probability of nighttime hypertension/non-dipping and, therefore, this symptom could warn about the presence or a bad control of hypertension at night in patients with severe OSA and nighttime hypoxemia. Further prospective studies, with a larger sample size, are needed to confirm these results.

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