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Hypoxemia and hypertension in obstructive sleep apnea: the forgotten variable

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TO THE EDITOR:

The apnea-hypopnea index (AHI), expressed as events/h, is used in order to define normality and to classify the severity of obstructive sleep apnea (OSA).[1] AHI measures the frequency of respiratory events throughout the night and the degree of sleep fragmentation, since apnea/hypopnea events are frequently followed by an electroencephalographic reaction. In addition, AHI gives us indirect information about hypoxemia, because respiratory events are often accompanied by a variable decrease in SpO_2.[2] The proportion of time spent in SpO_2 ≤ 90% (T90) is an accurate parameter to assess nighttime hypoxemia, since a 90% SpO_2 at sea level equals a PaO_2 of approximately 60 mmHg according to the oxygen-hemoglobin dissociation curve.[2] The correlation between AHI and T90 is moderate (r = 0.6-0.7), because not all respiratory events are followed by a drop in SpO_2 ≤ 90%.

OSA has been identified as a risk factor for hypertension in population-based studies.[3,4] Underlying mechanisms would be related to sympathetic activity secondary to hypoxia/hypercapnia cycles, increased intrathoracic pressure, and microarousals that follow apneas/hypopneas, which favor an increase in blood pressure.[4] Both animal and human studies have shown that intermittent hypoxemia can trigger hypertension.[4] Similarly to the hypothesis of other authors, ours was that T90 might be associated to hypertension in OSA patients.

In a preliminary and retrospective study based on the systematic collection database from the *Hospital Británico* of Buenos Aires sleep unit between 2011 and 2019, we included consecutive adult patients who underwent home-based respiratory polygraphy due to suspicion of OSA according to the results in the Berlin questionnaire (high risk), the Epworth Sleepiness Scale (ESS; > 10 points), or the STOP-Bang questionnaire (> 3 components). The study was approved by the institutional research ethics committee and the *Plataforma de Registro Informatizado de Investigaciones en Salud de Buenos Aires* in accordance with the standards of the Declaration of Helsinki, as amended (protocol #1242).

The diagnosis of hypertension was considered when it was self-referred, whether it was documented in the medical records, or whether the patient was on antihypertensive medication. These diagnostic strategies for hypertension have been validated and showed a good performance.[5] Automatic signal analysis was performed by trained physicians and was followed by manual corrections based on international criteria.[6] We calculated the T90 in % and the number of oxygen desaturations ≥ 3% (ODI, oxygen desaturation index) over valid recording time, after sequential manual revision. Multiple logistic regression analysis was used in order to establish the relationship between hypertension (dependent variable) and age, sex, BMI, AHI, and T90 (independent variables). For this purpose, study physicians performed a ROC analysis to establish the best cutoffs to differentiate between patients with and without hypertension. Predictive models also relied on traditional cutoffs, such as AHI (≥ 10 and ≥15 events/h).

We included 3.854 patients (median age = 55 years) who were mostly male (61.5% vs. 38.5%; p < 0.001). Prevalence of obesity and hypertension was 57.0% and 52.3%, respectively. In the study sample, 48% was classified as having moderate-to-severe OSA, and 29% of patients reported excessive daytime sleepiness (ESS > 10 points).

The best area under the ROC curve (AUC-ROC) to differentiate between patients with and without hypertension included the following cutoffs: age ≥ 52 years; BMI ≥ 30 kg/m^2; AHI ≥ 14 events/h; and T90 ≥ 3%. Table 1 presents multiple logistic regression models including AHI and T90: age (OR = 3.27-3.29; 95% CI: 2.83-3.80; p < 0.0001); male sex (OR = 1.34-1.35; 95% CI: 1.16-1.56; p < 0.001); BMI (OR = 1.82-1.83; 95% CI: 1.58-2.11; p < 0.0001); AHI (OR = 1.21-1.24; 95% CI: 1.03-1.45; p < 0.01); and T90 (OR = 1.54- – 1.57; 95% CI: 0.31-1.84; p < 0.0001).

Our main finding was that nighttime hypoxemia defined as T90 ≥ 3% was independently associated to the development of hypertension in OSA patients. This highlights the importance of nighttime hypoxemia as an independent risk factor for hypertension in patients with OSA, who represent the population of patients treated in a sleep unit. This observation was consistent after adjusting for other covariates (age, sex, BMI, and AHI), which is in line with experimental models that have established the role of hypoxemia as a mechanism of hypertension in OSA.[7,8] Two large studies reported that AHI ≥ 30 events/h and T90 ≥ 12%,[9] or quartiles 3 and 4 of ODI ≥ 4% (ODI4)[10] were independently associated with hypertension—T90 ≥ 12% (OR = 1.46; 95% CI: 1.12-1.88) and ODI4 (OR = 2.01; 95% CI: 1.6-2.5). In a study involving patients with moderate-to-severe OSA in use of CPAP,[8] CPAP was withdrawn for two weeks, and the patients were randomized to receive supplemental oxygen or air (sham) during sleep. Those who received supplemental oxygen had the rise in morning blood pressure virtually abolished.[8] Dean et al.[9] demonstrated that every standard deviation of increment

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Table 1. Multiple logistic regression predictive models for hypertension.

Variable	Coefficient	OR	95% CI	p
Model 1				
Age ≥ 52 years	1.19	3.3	2.86-3.80	< 0.0001
Male sex	0.34	1.4	1.2-1.6	< 0.0001
BMI ≥ 30 kg/m^2	0.63	1.9	1.6-2.2	< 0.0001
AHI ≥ 5 events/h	0.06	1.06	0.87-1.29	0.58
T90 ≥ 3%	0.52	1.7	1.45-1.96	< 0.0001
Model 2				
Age ≥ 52 years	1.18	3.27	2.83-3.77	< 0.0001
Male sex	0.30	1.35	1.17-1.56	< 0.0001
BMI ≥ 30 kg/m^2	0.60	1.83	1.59-2.11	< 0.0001
AHI ≥ 10 events/h	0.19	1.21	1.03-1.42	0.0205
T90 ≥ 3%	0.45	1.57	1.33-1.84	< 0.0001
Model 3				
Age ≥ 52 years	1.19	3.28	2.84-3.79	< 0.0001
Male sex	0.30	1.34	1.16-1.55	0.0001
BMI ≥ 30 kg/m^2	0.60	1.82	1.58-2.10	< 0.0001
AHI ≥ 14 events/h	0.22	1.24	1.07-1.45	0.0058
T90 ≥ 3%	0.43	1.54	1.31-1.81	< 0.0001
Model 4				
Age ≥ 52 years	1.19	3.29	2.85-3.80	< 0.0001
Male sex	0.30	1.35	1.17-1.56	0.0001
BMI ≥ 30 kg/m^2	0.60	1.83	1.59-2.11	< 0.0001
AHI ≥ 15 events/h	0.20	1.22	1.05-1.43	0.0112
T90 ≥ 3%	0.44	1.56	1.32-1.83	< 0.0001

AHI: apnea-hypopnea index; T90: proportion of total recording time with SpO_2 ≤ 90%.

in log-transformed hypoxic burden was associated with a 1.1% increase in systolic blood pressure and a 1.9% increase in diastolic blood pressure among those patients not using antihypertensive medications. Using a large cohort of moderate-to-severe OSA patients in South America, Labarca et al.[10] developed predictive models of cardiometabolic risk from indicators of hypoxemia (T90, minimum SpO_2 and ODI) and showed that a T90 > 10% was a predictor of arterial hypertension.

The limitation of the present study was that the diagnosis of hypertension was based on self-reporting, medical history records, or the history of antihypertensive drug use. However, despite this limitation, our observations are in line with the important body of experimental evidence in animals and humans that links intermittent hypoxemia with the development of hypertension.

In conclusion, nighttime hypoxemia defined as T90 ≥ 3% was an independent risk factor for hypertension in a clinical population of patients with suspected sleep apnea. This preliminary finding must be confirmed in prospective longitudinal studies.

Author contributions

Both authors participated in the drafting and revision of the manuscript, as well as in the approval of the final version.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Nogueira F, Nigro C, Cambursano H, Borsini E, Silio J, Avila J. Practical guidelines for the diagnosis and treatment of obstructive sleep apnea syndrome [Article in Spanish]. Medicina (B Aires). 2013;73(4):349-362.
2. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000;342(19):1378-1384. https://doi.org/10.1056/NEJM200005113421901
3. 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 [published correction appears in JAMA 2002 Oct 23-30;288(16):1985]. JAMA. 2000;283(14):1829-1836. https://doi.org/10.1001/jama.283.14.1829
4. Weiss JW, Tamisier R, Liu Y. Sympathoexcitation and arterial hypertension associated with obstructive sleep apnea and cyclic intermittent hypoxia. J Appl Physiol (1985). 2015;119(12):1449-1454. https://doi.org/10.1152/japplphysiol.00315.2015
5. Chrestani MA, Santos Ida S, Matijasevich AM. Self-reported hypertension: validation in a representative cross-sectional survey [Article in Portuguese]. Cad Saude Publica. 2009;25(11):2395-2406. https://doi.org/10.1590/S0102-311X2009001100010
6. Tkacova R, McNicholas WT, Javorsky M, Fietze I, Sliwinski P, Parati G, et al. Nocturnal intermittent hypoxia predicts prevalent hypertension in the European Sleep Apnoea Database cohort study. Eur Respir J. 2014;44(4):931-941. https://doi.org/10.1183/09031936.00225113

7. Tamisier R, Pépin JL, Rémy J, Baguet JP, Taylor JA, Weiss JW, et al. 14 nights of intermittent hypoxia elevate daytime blood pressure and sympathetic activity in healthy humans. Eur Respir J. 2011;37(1):119-128. https://doi.org/10.1183/09031936.00204209
8. Turnbull CD, Sen D, Kohler M, Petousi N, Stradling JR. Effect of Supplemental Oxygen on Blood Pressure in Obstructive Sleep Apnea (SOX). A Randomized Continuous Positive Airway Pressure Withdrawal Trial. Am J Respir Crit Care Med. 2019;199(2):211-219. https://doi.org/10.1164/rccm.201802-0240OC
9. Dean DA, Wang R, Jacobs DR, Duprez D, Punjabi NM, Zee PC, et al. A systematic assessment of the association of polysomnographic indices with blood pressure: the Multi-Ethnic Study of Atherosclerosis (MESA). Sleep. 2015;38(4):587-596. https://doi.org/10.5665/sleep.4576
10. Labarca G, Dreyse J, Salas C, Letelier F, Schmidt A, Rivera F, et al. Clinical utility of oximetric parameters to identify a high-risk phenotype of moderate-severe Obstructive Sleep Apnea (OSA). Clin Respir J. 2020;14(12):1166-1175. https://doi.org/10.1111/crj.13256