



Editorial

Treatment-Refractory Hypertension and Sleep Apnea. One Step Further[☆]

Hipertensión refractaria al tratamiento y apnea del sueño. Un paso más allá

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Enough evidence has been accumulated in 2 decades of clinical studies to confirm that obstructive sleep apnea (OSA) is associated with a higher prevalence and incidence of arterial hypertension (HT).¹ This partnership is underpinned by a solid pathophysiologic basis that points towards sympathetic hyperstimulation produced by respiratory events during sleep as the key underlying mechanism, modulated by the severity of the OSA, its symptoms, baseline blood pressure (BP) levels, and the age of the subjects.² International guidelines have very good reasons to consider OSA as a cause of HT, and recommend a sleep study as part of the etiological algorithm of HT in certain circumstances.^{3,4} Various meta-analysis have shown that treatment with continuous positive airway pressure (CPAP) reduces both systolic and diastolic BP by around 2–2.5 mmHg and 1–1.5 mmHg, respectively.⁵ Although these declines are modest, they are clinically significant in the long term, and similar to those achieved by other therapeutic measures.^{3,4}

Some of the most important epidemiological problems of HT, apart from its increasing incidence, are the high percentage of patients who remain uncontrolled and the difficulty encountered in identifying the reasons for this lack of control.⁶ Although this is due in most cases to a lack of diagnosis or inappropriate treatment, at other times the cause lies in the nature of the HT itself. Resistant HT (R-HT) is defined as HT that remains uncontrolled despite the administration of full doses of at least 3 antihypertensive drugs (or controlled with the administration of at least 4), one of which is ideally a diuretic. R-HT can account for up to 12%–15% of all forms of hypertension.⁷ OSA is highly prevalent among these patients (greater than 70%)⁸ and CPAP treatment has a positive effect on BP figures that is even greater than in other hypertensive patients (mean decreases in BP of about 4–5 mmHg).⁹ However, the role of CPAP in the long-term prognosis of these individuals is

not yet known. In an attempt to answer this question, the SEPAR Spanish Sleep Group has launched 2 important studies: the long-term follow-up of patients in the HIPARCO clinical trial¹⁰ which began in 2008 and in which data have already been collected from almost a decade of follow-up; and the SARAH study,¹¹ a multinational prospective observational study that expects to recruit more than 600 patients with R-HT with a follow-up of at least 4–5 years.

A further step has recently been taken in the classification of patients with uncontrolled BP. The University of Alabama group led by David Calhoun defined a group of patients with uncontrolled BP despite the use of practically all the available therapeutic arsenal (at least 5 antihypertensive drugs), in the absence of a secondary cause to explain the situation. This type of hypertension is called treatment-refractory HF (RF-HT). Although its prevalence is low (3%–9% of all cases of R-HT), these patients have a very high cardiovascular risk. Some authors postulate that it could represent a different HT clinical phenotype that might even have a characteristic endotype, since refractoriness to treatment could be due more to a failure to control sympathetic hyperstimulation than to overactivation of the renin-angiotensin-aldosterone system and the resulting water retention (a mechanism that seems more associated with R-HT than with RF-HT).¹²

In spite of the short scientific history of RF-HT, an investigation of a possible relationship with OSA would be interesting, given that sympathetic hyperstimulation is the pathophysiological mechanism in both diseases. The only study in this area, recently published, found that the prevalence of OSA in these patients is even higher than that observed in R-HT (95% of patients had AHI>15, and more than 60% had AHI>30). Patients with RF-HT were almost twice as likely to have an OSA syndrome, as well as increased heart rate and variable mean BP figures (as markers of sympathetic hyperstimulation) compared to patients with R-HT.¹³ These findings clearly raise quite a number of questions about the possible relationship between OSA and RF-HT: does OSA really have a special role in the genesis and the control of this particular type of “malignant” hypertension?; what factors influence this association?; what is the role of obesity as an intermediate variable?; can CPAP control BP better than medical treatment?; what

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is the best antihypertensive therapy in patients whose OSA must be treated with CPAP?; how does the presence of OSA and CPAP treatment affect patients' prognosis?; what makes a patient with R-HT develop RF-HT? Completed or ongoing studies on the relationship between OSA and HT could be the basis for the analysis of this special subgroup of patients with RF-HT. Such analyses would shed light on the hypothetical relationship between RF-HT and OSA, and could be the starting point for designing specific studies in this population which, given the low prevalence of the entity, would most likely have to be multicenter, and possibly multinational trials. In view of the limited therapeutic possibilities available for these patients, and their high cardiovascular risk, it seems legitimate to investigate the relationship of RF-HT with OSA in more depth, since, apart from the exciting scientific challenge that this entails, our patients could potentially obtain therapeutic and prognostic benefit.

References

1. Javaheri S, Barbe F, Campos-Rodríguez F, Dempsey JA, Khayat R, Javaheri S, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol*. 2017;69:841–58.
2. Sánchez de la Torre M, Campos-Rodríguez F, Barbé F. Obstructive sleep apnoea and cardiovascular disease. *Lancet Respir Med*. 2013;1:61–72.
3. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al., Task Force Members. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1925–38.
4. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al., Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–52.
5. Fava C, Dorignoni S, Dalle Vedove F, Danese E, Montagnana M, Guidi GC, et al. Effect of CPAP on blood pressure in patients with OSA/hypopnea. A systematic review and meta-analysis. *Chest*. 2014;145:762–71.
6. Pereira M, Lunet N, Azevedo A, Barros H. Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. *J Hypertens*. 2009;27:963–75.
7. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of Council for High Blood Pressure Research. *Circulation*. 2008;117:e510–26.
8. Muxfeldt ES, Margallo VS, Guimarães GM, Salles GF. Prevalence and associated factors of obstructive sleep apnea in patients with resistant hypertension. *Am J Hypertens*. 2014;27:1069–78.
9. Mo L, He QY. Effect of long-term continuous positive airway pressure ventilation on blood pressure in patients with obstructive and resistant hypertension: a meta-analysis of randomized controlled trial. *J Clin Hypertens (Greenwich)*. 2016;18:153–8.
10. Martínez-García M-A, Capote F, Campos-Rodríguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, et al., Spanish Sleep Network. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension the HIPARCO randomized clinical trial. *JAMA*. 2013;310:2407–15.
11. Sapiña-Beltrán E, Torres G, Martínez-Alonso M, Sanchez de la Torre M, Franch M, Bravo C, et al. Rationale and methodology of the SARAH trial: long-term cardiovascular outcomes in patients with resistant hypertension and obstructive sleep apnea. *Arch Bronconeumol*. 2018, <http://dx.doi.org/10.1016/j.arbres.2018.03.002>. pii:S0300-2896(18)30142-X [in English, Spanish].
12. Dudenbostel T, Siddiqui M, Oparil S, Calhoun DA. Refractory hypertension: a novel phenotype of antihypertensive treatment failure. *Hypertension*. 2016;67:1085–92.
13. Martínez-García MA, Navarro C, Torres G, Barbe F, Caballero C, Lloberes P, et al. Beyond resistant hypertension: relationship between refractory hypertension and obstructive sleep apnea. *Hypertension*. 2018;72:618–24.