

POINT:

Should Sleep Studies Be Performed for All Patients With Poorly Controlled Hypertension? Yes



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ABBREVIATIONS: DBP = diastolic BP; ITT = intention-to-treat; RCT = randomized controlled trial; RH = resistant hypertension; SBP = systolic BP

Resistant hypertension (RH) is characterized by a lack of appropriate BP control despite the use of three antihypertensive drug classes (commonly including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system, and a diuretic) in optimized doses. This definition also comprises patients whose BP is controlled by using four or more classes (assuming a lack of control when these patients were using three drug classes).¹ An extreme phenotype of RH, namely refractory hypertension, has gained recent interesting the literature to nominate patients with uncontrolled hypertension despite using five classes.² Current statistics using appropriately selected patients highlight that true RH represents roughly between 10% and 20% of patients with hypertension,^{3,4} and decades of trends suggest that RH is a growing condition in the hypertension field⁴ associated with poor prognosis.⁵

It is well established that hypertension is a multifactorial condition, with environmental factors and genetic

interactions playing a major role. Among patients with RH, it is important to determine whether there are specific causes that may help to explain the unusual BP behavior, the so-called secondary causes of hypertension.¹ A previous investigation screening all causes of secondary hypertension in consecutive cases of confirmed RH from two centers found that moderate to severe OSA was present in 64% of patients.⁶ Other investigations found similar alarming results (up to 83%),^{7–9} including in those with refractory hypertension.¹⁰ These numbers are much higher than the frequency of OSA among patients with overall hypertension (ranging from 30% to 56%).^{11,12} Recent evidence indicates that in participants with moderate or severe OSA, there was a 2.0 times higher odds of RH in black subjects.¹³ Potential explanations for this scenario include the huge percentage of obesity in RH and the role of nocturnal rostral fluid shift predisposing to upper airway collapse during sleep.¹⁴

Previous evidence suggests that OSA is not an innocent bystander in patients with RH. The RESIST-POL study showed that nighttime BP and moderate to severe OSA were independently associated with concentric hypertrophy and systolic dysfunction in patients with RH.^{15,16} There is also a body of evidence indicating that the treatment of OSA with CPAP reduces BP, especially in patients with uncontrolled BP, which includes patients with an impaired dipping pattern (< 10% reduction in BP during sleep compared with during the awake period)¹⁷ and patients with RH.^{18–21}

In scenarios where there is a high prevalence of a treatable disease that may potentially influence the course of the primary disease, it is strongly recommended to screen for OSA in all patients with RH. Unfortunately, available questionnaires will not be sufficient. Both the Berlin Questionnaire²² and the NoSAS score²³ seem to have poor accuracy in identifying patients at high risk of experiencing OSA.^{24,25} There are potential reasons for these poor performances. One of the domains of the Berlin Questionnaire is the presence of hypertension (which may contribute to overestimations of the rate of high-risk patients). It also includes subjective questions about factors such as daytime sleepiness that may not be present in a significant proportion of patients with OSA.²⁴ The NoSAS score includes questions that are more objective but devotes significant attention to the

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presence of adiposity parameters.²³ Although overweight and obesity are well-established risk factors for OSA, a recent investigation found no differences in BMI in RH patients with and without OSA.²⁵ This factor may contribute to the observed low accuracy of the NoSAS score in detecting OSA in these patients. Nondipping BP patterns might be useful in screening OSA, but it will not solve the problem because a significant proportion of patients with OSA present with a normal BP pattern.²⁶ Nevertheless, it is obvious that the development of validated and useful screening tools for OSA are highly desirable in patients with RH.

Therefore, the bottom line is thus: OSA seems to be extremely common and associated with target organ damage in RH but is clearly underdiagnosed in clinical practice (and the available questionnaires are not useful). How should we deal with this situation? Is it worthy to investigate (and treat) OSA in patients with RH? If so, how to do it? We still have no definitive answers on these matters, including the economic impact of this potential recommendation. As previously mentioned, CPAP promotes reductions in BP values, but the related absolute BP decreases seem to be modest (approximately 5 mm Hg for systolic BP in a meta-analysis)²¹ and did not promote BP control or reverse RH diagnosis in a significant proportion of patients. However, its impact cannot be ignored. From an epidemiologic point of view, BP reductions from 1 mm Hg are associated with improved cardiovascular prognosis, with obvious economic impact.²⁷ It is noteworthy that some patients may exhibit a huge decrease in BP following CPAP, and continued efforts to identify these patients may help to establish priorities for OSA diagnosis.²⁰ Some may argue that the long waiting lists for standard polysomnography and the lack of symptoms in a significant proportion of patients with RH may impose significant obstacles for appropriate adherence to OSA treatment and therefore to recommendations regarding routine investigation of OSA. We cannot ignore, however, that use of portable home monitors for OSA diagnosis is increasing. The ongoing Morbidity in Patients With Hypertension and Obstructive Sleep Apnea (MORPHEOS) trial²⁸ is addressing the validation of portable sleep monitors in diagnosing OSA in patients with uncontrolled BP, including in those with confirmed RH. In addition, great advancements have occurred in wearable devices for snoring and OSA detections.²⁹

Although there is still much work ahead in consolidating this type of technology in the sleep medicine field, we

cannot deny that it is only a matter of time before it is incorporated into clinical practice at a low cost. Finally, one should be cautious in assuming that the lack of subjective symptoms translates into a “benign” OSA. Generally speaking, many patients may adapt their lifestyle to chronic conditions and only perceive improvements in quality of life following initiation of treatment. From the cardiovascular perspective, despite some evidence suggesting that the impact of CPAP in asymptomatic or minimally symptomatic patients with OSA may not translate into cardiovascular benefits, this fact may partially be explained by the lack of good adherence to CPAP, rather than a lack of impact of asymptomatic OSA.³⁰ This important research area still lacks definitive evidence. Conversely, it also underscores the need for new effective treatments to surpass the CPAP challenges, especially in the long-term follow-up of OSA treatment.

In conclusion, despite the lack of definitive evidence regarding the role of OSA in RH, growing evidence indicates that OSA is more than a common condition or an epiphenomenon of obesity, a condition frequently observed in RH. The goal of the ongoing Long-Term Cardiovascular Outcomes in Patients With Resistant Hypertension and Obstructive Sleep Apnea (SARAH) cohort trial is to evaluate whether OSA is associated with poor prognosis in RH.³¹ In the meantime, we share the opinion that all patients with a confirmed RH diagnosis should undergo a formal sleep study (polysomnography or portable sleep monitor) because the available screening questionnaires are not helpful for these patients. The impact of CPAP on BP cannot be ignored in patients with RH as well as the potential effects of OSA treatment on other domains such as snoring, sleepiness, mood, nocturia, and sexual dysfunction.³⁰ Some of them may not be obviously related to OSA, which could explain the lack of impetus to investigate and treat sleep-disordered breathing in patients who have no daytime sleepiness (which frequently is the only criterion used for defining asymptomatic OSA). Last, but not least, OSA promotes sleep disruptions in bed-partners, including bed-partners of patients with RH, and may have significant consequences for long-term quality of life.

References

1. Carey RM, Calhoun DA, Bakris GL, et al; American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension*. 2018;72(5):e53-e90.

2. Dudenbostel T, Siddiqui M, Oparil S, Calhoun DA. Refractory hypertension: a novel phenotype of antihypertensive treatment failure. *Hypertension*. 2016;67(6):1085-1092.
3. Krieger EM, Drager LF, Giorgi DMA, et al; ReHOT Investigators. Spirinolactone versus clonidine as a fourth-drug therapy for resistant hypertension: the ReHOT Randomized Study (Resistant Hypertension Optimal Treatment). *Hypertension*. 2018;71(4):681-690.
4. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. *Circulation*. 2011;124(9):1046-1058.
5. Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation*. 2012;125(13):1635-1642.
6. Pedrosa RP, Drager LF, Gonzaga CC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. *Hypertension*. 2011;58(5):811-817.
7. Florkczak E, Prejbisz A, Szwencz-Pietrasz E, et al. Clinical characteristics of patients with resistant hypertension: the RESIST-POL study. *J Hum Hypertens*. 2013;27(11):678-685.
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(8):1069-1078.
9. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens*. 2001;19(12):2271-2277.
10. Martínez-García MA, Navarro-Soriano C, Torres G, et al; on behalf of the Spanish Sleep Network. Beyond resistant hypertension. Relationship between refractory hypertension and obstructive sleep apnea. *Hypertension*. 2018;72(3):618-624.
11. Sjöström C, Lindberg E, Elmasry A, Hägg A, Svärdsudd K, Janson C. Prevalence of sleep apnoea and snoring in hypertensive men: a population based study. *Thorax*. 2002;57(7):602-607.
12. Drager LF, Genta PR, Pedrosa RP, et al. Characteristics and predictors of obstructive sleep apnea in patients with systemic hypertension. *Am J Cardiol*. 2010;105(8):1135-1139.
13. Johnson DA, Thomas SJ, Abdalla M, et al. Association between sleep apnea and blood pressure control among blacks: Jackson Heart Sleep Study. *Circulation*. 2019;139(10):1275-1284.
14. Friedman O, Bradley TD, Chan CT, Parkes R, Logan AG. Relationship between overnight rostral fluid shift and obstructive sleep apnea in drug-resistant hypertension. *Hypertension*. 2010;56(6):1077-1082.
15. Dobrowolski P, Prejbisz A, Klisiewicz A, et al. Determinants of concentric left ventricular hypertrophy in patients with resistant hypertension: RESIST-POL study. *Hypertens Res*. 2015;38(8):545-550.
16. Dobrowolski P, Klisiewicz A, Florkczak E, et al. Independent association of obstructive sleep apnea with left ventricular geometry and systolic function in resistant hypertension: the RESIST-POL study. *Sleep Med*. 2014;15(11):1302-1308.
17. Castro-Grattoni AL, Torres G, Martínez-Alonso M, et al. Blood pressure response to CPAP treatment in subjects with obstructive sleep apnoea: the predictive value of 24-h ambulatory blood pressure monitoring. *Eur Respir J*. 2017;50(4). pii: 1700651.
18. Pedrosa RP, Drager LF, De Paula LKG, Amaro ACS, Bortolotto LA, Lorenzi-Filho G. Effects of OSA treatment on BP in patients with resistant hypertension: a randomized trial. *Chest*. 2013;144(5):1487-1494.
19. Martínez-García MA, Capote F, Campos-Rodríguez F, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. *JAMA*. 2013;310(22):2407-2415.
20. de Oliveira AC, Martinez D, Massier D, et al. The antihypertensive effect of positive airway pressure on resistant hypertension of patients with obstructive sleep apnea. *Am J Respir Crit Care Med*. 2014;190(3):345-347.
21. Liu L, Cao Q, Guo Z, Dai Q. Continuous positive airway pressure in patients with obstructive sleep apnea and resistant hypertension: a meta-analysis of randomized controlled trials. *J Clin Hypertens (Greenwich)*. 2016;18(2):153-158.
22. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med*. 1999;131(7):485-491.
23. Marti-Soler H, Hirotsu C, Marques-Vidal P, et al. The NoSAS score for screening of sleep-disordered breathing: a derivation and validation study. *Lancet Respir Med*. 2016;4(9):742-748.
24. Margallo VS, Muxfeldt ES, Guimarães GM, Salles GF. Diagnostic accuracy of the Berlin Questionnaire in detecting obstructive sleep apnea in patients with resistant hypertension. *J Hypertens*. 2014;32(10):2030-2036.
25. Giampá SQ, Pedrosa RP, Gonzaga CC, et al. Performance of NoSAS score versus Berlin Questionnaire for screening obstructive sleep apnoea in patients with resistant hypertension. *J Hum Hypertens*. 2018;32(7):518-523.
26. Genta-Pereira DC, Furlan SF, Omote DQ, et al. Nondipping blood pressure patterns predict obstructive sleep apnea in patients undergoing ambulatory blood pressure monitoring. *Hypertension*. 2018;72(4):979-985.
27. Hardy ST, Loehr LR, Butler KR, et al. Reducing the blood pressure-related burden of cardiovascular disease: impact of achievable improvements in blood pressure prevention and control. *J Am Heart Assoc*. 2015;4(10):e002276.
28. ClinicalTrials.gov. Morbidity in Patients With Hypertension and Obstructive Sleep Apnea (MORPHEOS). NCT02270658.
29. Shelgikar AV, Anderson PF, Stephens MR. Sleep tracking, wearable technology, and opportunities for research and clinical care. *Chest*. 2016;150(3):732-743.
30. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S; INCOSACT Initiative (International Collaboration of Sleep Apnea Cardiovascular Trialists). Sleep apnea and cardiovascular disease: lessons from recent trials and need for team science. *Circulation*. 2017;136(19):1840-1850.
31. Sapiña-Beltrán E, Torres G, Martínez-Alonso M, 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;54(10):518-523.

COUNTERPOINT: Should Sleep Studies Be Performed for All Patients With Poorly Controlled Hypertension? No



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The most studied and well-characterized phenotype of the “difficult-to-control” or “poorly controlled” patient with hypertension is the so-called resistant hypertension (RH).

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