Filling in the Pieces of the Sleep Apnea–Hypertension Puzzle

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OBSTRUCTIVE SLEEP APNEA (OSA) IS A COMMON BUT underdiagnosed disorder that is associated with excessive sleepiness, poor quality of life, neurocognitive deficits, metabolic dysfunction, cardiovascular disease, and early mortality. Continuous positive airway pressure (CPAP) therapy efficaciously ameliorates obstructed breathing events.[1] Randomized controlled trials (RCTs) show that CPAP therapy reduces sleepiness and improves quality of life in patients with moderate and severe OSA.[2] A number of difficulties have complicated the assessment of the causal link between OSA and hypertension, including multiple shared risk factors, differential susceptibility of subgroups to the deleterious effects of OSA, and the challenges of conducting definitive RCTs. Despite these barriers, a significant evidence base has developed to support the identification and treatment of OSA in patients with hypertension. Multiple hypertension guidelines recognize OSA as a secondary cause of hypertension and specifically advise assessment and treatment of OSA in patients with refractory hypertension.[3-5]

Data largely support a causal link between OSA and hypertension, with causation supported by the Bradford-Hill criteria of (1) biological plausibility; (2) association strength, consistency, temporality, and dose response; and (3) reversibility. It is biologically plausible that OSA may cause hypertension, because intermittent hypoxia and sleep disruption (as in OSA) stimulate sympathetic excitation and hypertension acutely, and alter vascular resistance, increase blood pressure, and produce endothelial dysfunction chronically.[6] Evidence of association from longitudinal epidemiologic studies complements the biological data. The Wisconsin Sleep Cohort Study of middle-aged adults found a strong dose-response relationship between baseline OSA severity and incident hypertension 4 years later.[7] The Sleep Heart Health Study analysis of older adults without hypertension also found a dose-response relationship between baseline OSA severity and incident hypertension, but the association was not statistically significant in the fully adjusted analysis[8]; however, more than 50% of the original cohort was excluded because of baseline hypertension. Together, these findings are consistent with a modest association between OSA and incident hypertension that is confounded by obesity and is difficult to detect in certain subgroups (eg, older adults).

Reversibility of increased blood pressure has been tested in a number of RCTs of CPAP effect. Despite some variability in findings, individual studies and meta-analyses[9,10] have shown modest decreases in mean blood pressure (approximately 2 mm Hg) with CPAP treatment. Greater effects occurred in participants with higher CPAP therapy adherence, higher baseline blood pressure, more severe OSA, and more sleepiness as measured by a higher Epworth Sleepiness Scale score. Conversely, a study by Barbé et al[11] found that blood pressure did not significantly decrease in 55 nonsleepy (Epworth Sleepiness Scale score <11) patients with normal mean baseline blood pressure, despite severe OSA. In contrast to effects on blood pressure, few studies have assessed whether CPAP therapy reduces incident hypertension.[12]

Two studies in this issue of *JAMA* address the relationships among OSA, CPAP therapy, and incident hypertension and cardiovascular events. The observational study by Marin et al[13] measured the association between OSA and incident hypertension and tested the hypothesis that adherent CPAP therapy reduces the risk of incident hypertension. With a median 12.2 years of follow-up, the study found a strong dose-response relationship between OSA and incident hypertension and a strong association between adherent CPAP therapy use and lower incidence of hypertension, after adjustment for important known confounders. The RCT by Barbé et al[14] tested the effect of CPAP prescription on incident hypertension and cardiovascular events in nonsleepy patients with OSA. The investigators found a treatment effect over a median of 2.7 years of follow-up that did not reach statistical significance. Taken together, these studies augment the evidence that the presence of OSA poses a risk for incident hypertension and provide strong but not definitive evidence that CPAP therapy may reduce the risk. In nonsleepy patients with OSA, the effect of CPAP therapy prescription remains unclear.

The cohort study by Marin et al[13] is vulnerable to threats to internal validity (eg, selection bias among those participants enrolled, healthy user effect, and residual confounding), but it carries greater external validity (generalizability) than the RCT and it represents strong (level 2) evidence.[15] This

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observational study design offers important advantages when an RCT is not ethical (eg, clinical equipoise lacking) or feasible (eg, inadequate enrollment, sample size, or follow-up duration). These advantages and limitations were reflected in their results, which showed that the group adherent to CPAP therapy had a significantly lower risk of incident hypertension compared with untreated patients with OSA, although the effect could not definitively be attributed to CPAP therapy use.

The study by Barbé et al[14] focused on nonsleepy patients, for whom there was clinical equipoise regarding CPAP benefits,[11] permitting the ethical use of an RCT design. This design has the strongest internal validity, representing level 1 evidence,[15] because it avoids many biases that threaten internal validity, and it balances known and unknown confounders. However, statistical power was limited because (1) the anticipated effect size was overestimated by extrapolation from a sleepy cohort of adherent CPAP users with 10.1-year follow-up[16]; (2) 53% of the patients treated with CPAP therapy had baseline hypertension and were eligible only for the rare incident cardiovascular event outcome; and (3) outcomes were assessed over a short period for incident hypertension or cardiovascular events (median, 2.7 years). The point estimate of CPAP therapy effect (incidence density ratio, 0.83 vs control) was clinically important; therefore, the statistically negative result might be due in part to insufficient statistical power.

Further complicating interpretation of the findings, the intention-to-treat analysis tested whether prescription rather than use of CPAP therapy improved outcome. Nonadherence to CPAP therapy is common, yet CPAP effect is dose-dependent.[10] In this RCT, 36% of patients used CPAP therapy less than 4 hours per night on average, a threshold often used to define minimum acceptable CPAP use. A post hoc analysis stratifying on this CPAP use threshold showed a clinically important and statistically significant reduction in incident hypertension with CPAP use. This result is hypothesis-generating because it was not part of the a priori analysis plan, but it is consistent with other dose-response clinical benefits of CPAP therapy.[10,13] In conclusion, the study by Barbé et al[14] does not rule out a treatment effect of CPAP therapy in nonsleepy patients with OSA and instead suggests there may be an effect if CPAP adherence is adequate.

Although these studies significantly advance the understanding of the positive relationship between OSA and incident hypertension and the benefit of CPAP therapy, many questions remain regarding OSA, hypertension, and treatment. What are the susceptible and responsive subgroups (eg, OSA severity subgroups, sleepy vs nonsleepy, and demographic subgroups)? How much CPAP use is necessary for an important treatment effect? What are the effects of other OSA treatments? These questions will require RCTs when feasible, subgroup analyses within these trials, and well-controlled observational studies. Novel approaches are needed, such as treatment withdrawal protocols.

Despite these questions, considerable evidence supports the role of identification and treatment of OSA to improve symptoms, quality of life, and cardiovascular end points. More specifically, data generally support a causal link with hypertension. Treatment may not only reduce blood pressure (although modestly on average), but if confirmed by future studies also may prevent hypertension in at-risk patients. Thus, OSA deserves attention in patients with or at risk of developing hypertension as a potentially treatable cause of hypertension as well as other clinically important outcomes.

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REFERENCES

1. Balk EM, Moorthy D, Obadan NO, et al. *Diagnosis and Treatment of Obstructive Sleep Apnea in Adults: Comparative Effectiveness Review No. 32* (Prepared by Tufts Evidence-Based Practice Center under contract 290-2007-10055-1): AHRQ publication 11-EHC052-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2011.
2. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev*. 2006;3(3):CD001106.
3. Rabi DM, Daskalopoulou SS, Padwal RS, et al. The 2011 Canadian Hypertension Education Program recommendations for the management of hypertension: blood pressure measurement, diagnosis, assessment of risk, and therapy. *Can J Cardiol*. 2011; 27(4):415-433, e1-e2.
4. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation*. 2008;117(25):e510-e526.
5. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *J Am Coll Cardiol*. 2011;57(20):2037-2114.
6. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev*. 2010;90(1):47-112.
7. 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.
8. O'Connor GT, Caffo B, Newman AB, et al. Prospective study of sleep-disordered breathing and hypertension: the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2009;179(12):1159-1164.
9. Bazzano LA, Khan Z, Reynolds K, He J. Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension*. 2007; 50(2):417-423.
10. Haentjens P, Van Meerhaeghe A, Moscariello A, et al. The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome. *Arch Intern Med*. 2007;167(8):757-764.
11. Barbé F, Mayoralas LR, Duran J, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness: a randomized, controlled trial. *Ann Intern Med*. 2001;134(11):1015-1023.
12. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. *Am J Respir Crit Care Med*. 2002;166(2):159-165.
13. Marin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA*. 2012;307(20):2169-2176.
14. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *JAMA*. 2012;307(20):2161-2168.
15. Straus SE, Richardson WS, Glasziou P, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach It.* 4th ed. Edinburgh, Scotland: Churchill Livingstone Elsevier; 2011.
16. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005;365(9464):1046-1053.