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# Filling in the Pieces of the Sleep Apnea-Hypertension Puzzle

**Vishesh K. Kapur, MD, MPH**[1,2] and **Edward M. Weaver, MD, MPH**[2,3,4]

[1]Division of Pulmonary and Critical Care Medicine, University of Washington

[2]UW Medicine Sleep Center, University of Washington

[3]Surgery Service, Department of Veterans Affairs Medical Center, Seattle, Washington

[4]Department of Otolaryngology/Head & Neck Surgery, University of Washington

Obstructive sleep apnea (OSA) is a common but under-diagnosed disorder that is associated with excessive sleepiness, poor quality of life, neuro-cognitive 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 reduces sleepiness and improves quality of life in patients with moderate and severe OSA.[2] A number of challenges 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 defined by the Bradford-Hill criteria: biological plausibility; association strength, consistency, temporality and dose response; and 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 four years later.[7] The Sleep Heart Health Study analysis of non-hypertensive older adults 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

Corresponding Author: Edward M. Weaver, MD, MPH, VAPSHCS 112-OTO, 1660 S. Columbian Way, Seattle, WA 98018, eweaver@uw.edu, Phone: 206-764-2948, Fax: 206-764-2063.

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are consistent with a modest association between OSA and incident hypertension that it is confounded by obesity and is difficult to detect in certain subgroups (e.g., older adults)

Reversibility of blood pressure elevation 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 mmHg) with CPAP treatment. Greater effects occurred in participants with higher CPAP adherence, higher baseline blood pressure, more severe OSA, and more sleepiness as measured by higher Epworth Sleepiness Score (ESS). A study by Barbé et al found that blood pressure did not significantly decline in 55 non-sleepy (ESS<11) normotensive patients with severe OSA.[11] In contrast to effects on blood pressure, few studies have assessed whether CPAP reduces incident hypertension.[12]

Two studies in this issue of *JAMA* address the relationships among OSA, CPAP, 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 potential for adherent CPAP therapy to reduce 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 use and lower incidence of hypertension with adjustment for important known confounders. The RCT by Barbe et al.[14] tested the effect of CPAP prescription on incident hypertension and cardiovascular events in non-sleepy OSA patients. 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 OSA poses a risk for incident hypertension for OSA patients, and provide strong but not definitive evidence that CPAP may reduce the risk. In non-sleepy OSA patients, the effect of CPAP prescription remains unclear.

The cohort study by Marin et al[13] is vulnerable to threats to internal validity (e.g., selection bias among those 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 observational design offers important advantages when an RCT is not ethical (e.g., clinical equipoise lacking) or feasible (e.g., 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 had a significantly lower risk of incident hypertension compared to untreated OSA patients, although the effect could not definitively be attributed to CPAP use.

The study by Barbé et al[14] focused on non-sleepy patients, for whom there was clinical equipoise regarding CPAP benefits,[11] permitting the ethical use of a RCT design. This design has the strongest internal validity, representing level 1 evidence[15] as 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 unintentionally overestimated by extrapolation from a sleepy cohort of adherent CPAP users with 10.1-year follow up;[16] 2) 53% of the CPAP patients had baseline hypertension and were eligible only for the rare incident cardiovascular event outcome; and 3) outcomes were assessed over a short time period for incident hypertension or cardiovascular events (median

2.7 years). The point estimate of CPAP effect (incidence density ratio 0.83 compared to control) was clinically important, so 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 improved outcome. Non-adherence to CPAP is common, yet CPAP effect is dose dependent.[10] In this RCT, 36% of patients used CPAP 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.[10, 13] In summary, the study by Barbé et al does not rule out a treatment effect of CPAP in non-sleepy OSA patients and instead suggests there may be one 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, many questions remain regarding OSA, hypertension, and treatment. What are the susceptible and responsive subgroups (eg, OSA severity subgroups, sleepy versus non-sleepy, 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 endpoints. 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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