

The association of sleep disturbances measures with blood pressure: is the time to explore novel measurements?

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Obstructive sleep apnea (OSA) is a chronic disease that affects more than 15% of the adult population and becomes more prevalent with age.¹ Although multiple observational studies show that OSA is an independent risk factor for cardiovascular disease (CVD), the treatment of OSA with continuous positive airway pressure (CPAP) does not uniformly prevent CVD. Recent randomised clinical trials failed to demonstrate a role for CPAP treatment in secondary CVD prevention.^{2,3} Nevertheless, CPAP treatment affects cardiovascular outcomes positively in specific groups of OSA patients. For example, patients with resistant hypertension experience a significant reduction in 24-hour blood pressure with CPAP treatment.⁴ Notably, a secondary analysis of this study showed that CPAP treatment did not decrease blood pressure in at least 30% of patients with resistant hypertension, demonstrating that a more precise approach to patient selection is needed to improve the effectiveness of OSA treatment(s) in CVD prevention. Previous studies have explored novel approaches to identify OSA patients where CPAP treatment has significant antihypertensive effects. These studies have demonstrated a combination of specific biomarkers together with the clinical characterisation of circadian blood pressure patterns to be informative.^{5–7} In this context, the identification of new clinical variables that go beyond the apnea-hypopnea index (AHI), which fails to capture the complexity of OSA pathophysiology, may allow precise CVD risk stratification.

The results of a cross-sectional analysis of the Multi-Ethnic Study of Atherosclerosis community-based cohort are reported in the journal by Kim *et al.*⁸ The

study provides more insight into the role of OSA in hypertension by exploring unique measurements of sleep disturbance and its contribution to blood pressure levels. The authors evaluated different measures of sleep depth, upper airway resistance and severity of intermittent hypoxia related to obstructive respiratory events, as predictors of blood pressure. Presumably, these measures were chosen due to biological plausibility and the availability of validated software algorithms that circumvent issues such as interscorer reliability. While sleep depth, indicated by the 'OR product' (ORP), did not affect daytime blood pressure, air-flow limitation (duty cycle and inspiratory flow limitation) in non-rapid eye movement (NREM) sleep was associated with lower systolic blood pressure. The direction of this association was similar but weaker in REM sleep and not statistically significant for diastolic blood pressure. In contrast, hypoxia burden, resulting from apneas and hypopneas, was associated with significantly higher diastolic blood pressure, with effects noted on systolic blood pressure only in certain subgroups (mild OSA and no antihypertensive medication use). Previous community-based cross-sectional and longitudinal studies have shown that AHI and Epworth Sleepiness Scale (ESS) are OSA-specific predictors of blood pressure.^{9–11} This association is stronger in clinical populations with OSA and resistant hypertension.^{12,13} Nevertheless, the use of AHI and ESS as inclusion criteria in large scale effectiveness trials have resulted in modest effects on blood pressure, dampening the enthusiasm for OSA screening and management as a strategy for CVD mitigation.¹⁴ In our view, the two primary reasons for modest and variable effects of CPAP treatment on blood pressure across clinical trials are the imprecise definition of 'at-risk' population and suboptimal CPAP adherence. Prognostic physiological or genomic biomarkers predictive of OSA-related hypertension can address the first limitation. Such biomarkers can also help direct CPAP adherence promotion or alternative OSA and hypertension treatments to at-risk populations. Investigating potential prognostic biomarkers

of OSA-related hypertension in observational studies (vs in clinical trials) offers the advantage of separating the effects of the duration of treatment intervention and adherence. Hence, upper airway resistance without hypoxia and hypoxia burden as potential protective and detrimental physiological biomarkers for OSA-related hypertension, respectively, should be replicated in longitudinal studies and validated in clinical cohorts. The studies in clinical cohorts should be adequately powered to assess significant moderators of OSA-related hypertension, like baseline severity of disease and age.

Notable strengths of this study include a large and diverse sample, the use of multiple measures of upper airway resistance, and adjustment of main findings by AHI and hypertension medication use. The analytical approach of separating each of the polysomnography-derived predictors by NREM and rapid eye movement (REM) sleep stage is critical, given the distinct physiology of the autonomic and ventilatory systems during these sleep stages. Although the authors adjusted for age, if there was sufficient sample size in the 45–60 years' age-group, stratified analyses by age could be instructive regarding the lack of sleep depth effects on blood pressure. Given the ageing effects on sleep, ORP is likely not specific to OSA-related sleep disturbance in the older age-group. Moreover, the association between OSA and hypertension appears to attenuate after the age of 60 years.¹⁵ Thus, an examination of the polysomnography-derived predictors of blood pressure, particularly the ORP, in younger individuals, is warranted. In this regard, other novel measures from Younes *et al* may provide additional insights; ORP-9 (a measure of postarousal sleep dynamics) and peak-ORP during arousals reflecting the arousal intensity.¹⁶ The cross-sectional design precludes causal inferences but raises hypotheses regarding potentially protective and detrimental OSA-specific traits that plausibly affect blood pressure and can be derived easily from polysomnography in an automated and standardised manner across research studies. Few limitations of this study merit further discussion. As acknowledged by the authors, the primary outcome assessment of blood pressure is based on office measurement, instead of 24-hour ambulatory blood pressure measurement. Daytime blood pressure measurements at a single time-point may not be reflective of the 'true' physiological blood pressure status, for example, in patients with white-coat hypertension. Moreover, this

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approach fails to account for the impact of sleep disturbance -on circadian-related blood pressure dipping and nocturnal hypertension, potential phenotypic markers of OSA-related hypertension.⁷ Finally, the number of antihypertensive medications in the adjustment of measured blood pressure values or the effects of specific antihypertensive medications (eg, beta blockers) on sleep architecture was not considered. These analytical approximations could obscure some of the associations examined.

Given the complexity of OSA and the apparent need for a precision medicine approach to guide treatment and future research, now is the time to explore new measures of sleep disturbances as prognostic biomarkers. This study provides proof-of-concept that the recently developed polysomnographic measures of sleep depth, upper airway resistance and severity of intermittent hypoxia related to obstructive respiratory events may be predictive of daytime blood pressure. As a next step, it would be appropriate to replicate and extend the findings of this study with more robust (24 hours) blood pressure assessments and stratified analysis by age. This is necessary to demonstrate a valid prognostic contribution of these variables to CVD risk in OSA.

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