Sleep Apnea–Specific Hypoxic Burden and Not the Sleepy Phenotype as a Novel Measure of Cardiovascular and Mortality Risk in a Clinical Cohort

In this issue of the *Journal*, Trzepizur and colleagues (pp. 108–117) report associations of sleep apnea–specific hypoxic burden (HB) (1) and risk of cardiovascular events and all-cause mortality (2). In a clinical cohort of 5,358 patients with newly diagnosed obstructive sleep apnea (OSA) and no overt cardiovascular disease, HB (i.e., respiratory event–related area under desaturation curve) predicted incidence of major adverse cardiovascular events (MACE) (median follow up of 78 months). In adjusted survival analyses, there was a dose–response relationship between HB and MACE incidence even after accounting for lung disease and smoking history. This association was stronger in women than in men (*P* value for interaction = 0.03) and appeared stronger in younger (age, ⩽65 years) than older individuals (*P* value for interaction = 0.06). The interaction between sleepiness and HB was not tested; however, the "moderately sleepy (Epworth Sleepiness Scale [ESS] = 8 [5–11])" group had highest HB (53 [23–118]%minute/hour), followed by the "minimally symptomatic (ESS = 7 [4–9])," "excessively sleepy (ESS = 13 [11–16])," and "disturbed sleep (ESS = 6 [4–8])" groups.

In this work, HB appears to be underestimated for a clinical cohort (2). For example, in those with an apnea–hypopnea index (AHI) ⩾5 events/hour (similar inclusion criterion in the study by Trzepizur and colleagues) from the Sleep Heart Health Study, the AHI, time with oxygen saturation <90% (T90), and HB median (interquartile range) were 16 (10–27), 0.4% (0%–2.6%), and 42%min/h (26–69%min/h), respectively. In comparison, in the current study, the AHI, T90, and HB were 27 (14–42), 2% (0%–7%), and 32%min/h (13–71%min/h), respectively. Therefore, despite a higher degree of OSA severity in the current work, compared with the Sleep Heart Health Study findings, the degree of HB was lower. The discrepancy may be explained by differences in demographics/comorbidities—albeit observed directionality is not anticipated—or in a clinical cohort greater non-OSA hypoxic contribution, inclusion of home sleep apnea testing without electroencephalogram monitoring, and/or differences in analytic approach to the calculation of HB, including artifact rejection.

Nonetheless, these findings provide novel evidence of clinical utility of HB (designed to better capture total OSA-specific desaturation) to identify those with an increased risk of adverse health outcomes (1, 3–5). Other commonly used OSA severity metrics, such as AHI and oxygen desaturation index, that do not account for the duration and depth of desaturations were not associated with MACE. However, the authors reported that T90 also predicted the incidence of MACE. Although HB and T90 represent the total desaturation during sleep, the correlation between the two metrics was low in the original study (1). By removing the preevent baseline saturation, the effect of baseline saturation on HB was minimized. In contrast, for baseline saturations close to 90%, the T90 metric becomes highly sensitive to baseline saturation as well as other oximetry artifacts. Although T90 could potentially be used for cardiovascular disease risk stratification in pulmonary disease irrespective of sleep disordered breathing, it is nonspecific, as it captures sustained non-OSA–related hypoxemia, and therefore may not be an appropriate metric to gauge OSA-related risk. Furthermore, it depends on an arbitrary absolute threshold of 90%, which may not apply across populations. For example, T93 and not T90 was a predictor of mortality in women (6). Finally, although the authors revealed a stronger association of HB with MACE in women, further investigations are needed to determine the optimal threshold and clarify sex-specific differences.

In contrast to the compelling findings of HB as a relevant predictor of cardiovascular events, in this clinical cohort study, the authors did not identify clinical symptom-based phenotypes as predictors of cardiovascular outcomes in adjusted analyses, thus running counter to data from population-based studies. The minimally symptomatic group demonstrated increased cardiovascular event risk compared with other symptom subtypes in unadjusted analyses but not in adjusted analyses. The authors suggest that the comorbidities may be driving the unadjusted association potentially attributable to referral bias as reflective of a clinic-based sample with greater comorbidity burden.

The results of the current work emerge in the setting of a growing body of literature from population-based studies identifying the sleepy-based phenotypes in moderate to severe OSA and increased cardiovascular risk. The excessively sleepy phenotype was identified as a predictor of incident and recurrent cardiovascular events, albeit not for cardiovascular mortality (7). Also, clinical trials focused on minimally symptomatic participants or those without sleepiness have identified limited OSA treatment benefit on blood pressure and cardiovascular outcomes (8, 9). Potential explanations for inconsistencies in symptom-based findings of population-based studies versus this clinical cohort include *1*) healthy volunteer bias in epidemiologic studies versus referral bias in clinical cohorts, resulting in differential generalizability; *2*) variability in available symptoms and characterization of symptoms; *3*) residual confounding by inadequate accounting of competing risk factors for sleepiness (e.g., somnogenic medications, depression, or sleep quantity); and/or *4*) limitations of latent class analyses, including misclassification of class assignment and naming fallacy (i.e., class may not reflect the class membership) (10).

Overall, the current work elucidates the value of HB—and not symptom subtypes—in the prediction of cardiovascular events and

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mortality in a clinical cohort, thereby lending support to the utility of the novel HB measure in both the clinical and population health settings. These data underscore the importance of the role of nocturnal hypoxia specifically linked to OSA in portending cardiovascular risk. Future opportunities include clarifying explanatory sleep apnea–specific hypoxic mechanistic pathways contributing to cardiovascular risk. Given intermittent hypoxia in OSA has been implicated in impaired function of orexin (alerting) neurons (11), an enhanced understanding of the intersection of HB and symptom-based phenotypes will be useful to inform OSA risk stratification and potentially treatment responsiveness. ■

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2021 American Thoracic Society BEAR Cage Winning Proposal: Microbiome Transplant in Pulmonary Arterial Hypertension

What Is the Evidence that the Gut Microbiome Plays a Role in Pulmonary and Cardiovascular Disease?

The gut microbiome is integral to host physiology, including metabolism and immunity (1, 2). Interest in how the microbiome impacts chronic diseases, including chronic obstructive pulmonary disease, asthma, heart failure, idiopathic pulmonary fibrosis (3–5), and others, has been growing. Fecal microbiomes in patients with chronic obstructive pulmonary disease differ in relative abundances of several bacterial species and microbial metabolites compared with healthy control subjects (6). Lower fecal microbiota diversity, assessed by 16S rRNA gene sequencing within the first year of life, correlates with asthma development by age 7 years (7), and infants deemed to be at risk for asthma development have lower levels of the bacterial-produced, antiinflammatory, short-chain fatty acid (SCFA) acetate in their feces (8). Mice supplemented with SCFAs by including acetate in their drinking water develop significantly reduced lung inflammatory cellular infiltrates, whereas mice fed a low-fiber diet

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