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Sleep Apnea Heterogeneity, Phenotypes, and Cardiovascular Risk
Implications for Trial Design and Precision Sleep Medicine

Obstructive sleep apnea (OSA) affects 25 million adults in the United States and is linked to major causes of morbidity and mortality, including coronary heart disease, heart failure (HF), stroke, and atrial fibrillation (1–4). Importantly, patients with sleep apnea are heterogeneous with respect to symptoms, physiologic traits linked to disease pathogenesis, and the polysomnographic expression of this disorder (e.g., severity of hypoxemia and sleep architectural changes).

Despite this variability, clinical sleep medicine focuses on "cutoffs" or threshold values of a single metric (i.e., the apnea–hypopnea index [AHI]) for diagnosis and severity grading of OSA. However, these threshold values are not the best predictor of OSA-related morbidity, and the field is now questioning the use of the AHI as the primary diagnostic or prognostic criterion for patients with sleep-disordered breathing. Indeed, various health outcomes may be related to sleep apnea through distinct pathophysiologic pathways that differentially reflect responses to hypoxemia, arousal (5), and sleep state (6). Should we be using one, two, or more of these sleep-associated measures to follow patients with sleep apnea?

Recently, a number of studies have begun to leverage the inherent heterogeneity in OSA and shed light on this question by using methods that can be broadly classified as either supervised or unsupervised analytic approaches (7). Supervised approaches involve the evaluation of prespecified hypotheses and often involve traditional regression modeling methods applied to single or few features. Recent excellent examples of this approach include observations that REM sleep apnea (6) and hypoxic burden (8) significantly increase cardiovascular risk in patients with sleep apnea. In contrast, unsupervised methods focus on discovering emergent patterns within the data, often use cluster or neural network analyses, and examine many features to generate hypotheses. Applying this approach to various domains of polysomnographic variables, Zinchuk and colleagues observed that there were multiple clusters of patients within traditional AHI severity cutoff groups, and that some were significantly associated with adverse cardiovascular outcomes (9). Importantly, they found a variable responsiveness to continuous positive airway pressure (CPAP) therapy in attenuating cardiovascular risk among these clusters.

Together, these data may in part explain the negative findings of recent randomized controlled trials focused on cardiovascular outcomes (10, 11). In addition, these trials tended to focus on patients who were not excessively sleepy, given the ethical challenges posed by randomization of such individuals to receive no specific treatment (e.g., with respect to motor vehicle accident risk). Lack of sleepiness may have also contributed to lower than expected CPAP adherence (12), another plausible contributor to the null results of these trials.

It is in this context that Mazzotti and colleagues (pp. 493–506) present their paper entitled "Symptom Subtypes of Obstructive Sleep Apnea Predict Incidence of Cardiovascular Outcomes" in this issue of the *Journal* (13). In this study, the authors aimed to characterize OSA symptom subtypes and assess their association with prevalent and incident cardiovascular disease (CVD) in the successful community-based Sleep Heart Health Study. Using latent class analysis (an unsupervised approach), they observed four subtypes of symptoms: disturbed sleep (12.2%), minimally symptomatic (32.6%), excessively sleepy (16.7%), and moderately sleepy (38.5%). Similar symptom subtypes have been previously observed in other population-based (14) and clinical (15) samples, reinforcing their validity. In adjusted models, the "excessively sleepy" subtype was associated with a more than threefold increased risk of prevalent HF compared with each of the other subtypes. Symptom subtype was also associated with incident CVD ($P < 0.001$), coronary heart disease ($P = 0.015$), and HF ($P = 0.018$), with "excessively sleepy" again demonstrating increased risk (hazard ratios of 1.7–2.4) compared with other subtypes.

This study highlights the importance of considering symptom subtypes when designing trials to assess the cardiovascular benefits of CPAP treatment. For example, the RICCADSA (Continuous Positive Airway Pressure [CPAP] Treatment in Coronary Artery Disease and Sleep Apnea) study (11), a randomized trial in individuals with severe OSA who were not excessively sleepy, found no cardiovascular benefit of CPAP in intention to treat analyses. Similarly, the much larger SAVE (Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea to Prevent

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Cardiovascular Disease) trial in patients with known CVD excluded patients with Epworth Sleepiness Scale > 15 (10). Given their higher risk of OSA-related cardiovascular events (as observed by Mazzotti and colleagues), excluding excessively sleepy patients from randomized trials will limit investigators' ability to detect beneficial treatment effects, and may be an additional factor related to these negative trial results. Among excessively sleepy patients with sleep apnea, it is unknown whether CPAP reduces cardiovascular outcomes, and strategies to safely and ethically enroll such patients in future studies are greatly needed. Such methodologic approaches might include enhanced safety monitoring, strategies to mitigate drowsy driving, and propensity score matching.

Although the concept that patients with excessive sleepiness have increased cardiovascular risk is not new (16), the study by Mazzotti and colleagues indicates that the increased risk observed in the "excessively sleepy" phenotype may be a surrogate marker of underlying cardiovascular risk pathways influenced by OSA, rather than an independent risk factor in the absence of an elevated AHI. Understanding the physiologic basis for the different clinical symptom subtypes is an area of important future research. Such insights may come from "deep phenotyping" approaches that involve new measures of sleep apnea pathophysiology, such as arousability, ventilatory control sensitivity, upper airway collapsibility, and muscle compensation (17). Furthermore, exploring the relationship between excessive sleepiness and biological markers of oxidative stress and inflammation may also yield important insights (18). Approaches that take advantage of physiologic phenotyping and biomarkers are already proving useful for predicting responsiveness to various treatment modalities (19–22).

Together with previous works, this study by Mazzotti and colleagues indicates that the field of sleep medicine is taking the critical first steps toward applying precision medicine tools to patients with OSA in an attempt to understand their cardiovascular risk. Such approaches are bound to enable the design of more rigorous clinical trials and more personalized treatment approaches for our patients. ■

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