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Continuous Positive Airway Pressure and Cardiovascular Risk Reduction in Patients without Excessive Sleepiness

Importance of the Pulse Rate Response

Subgroup analyses of cardiovascular prevention trials in obstructive sleep apnea (OSA) may play an important role in patient selection for future trials. In the intention-to-treat analysis of the RICCADSA (Randomized Intervention with Continuous Positive Airway Pressure in coronary artery disease (CAD) and OSA) randomized controlled trial (RCT), CPAP failed to reduce adverse cardiovascular outcomes in nonsleepy patients with OSA and CAD (1). In this issue of the *Journal*, Azarbarzin and colleagues (pp. 767–774) report a secondary analysis of the RICCADSA RCT to test for heterogeneity of CPAP effect on the basis of pulse rate response to respiratory events (ΔHR) (2). Using a multivariable Cox regression as their

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primary analysis, the authors found that patients with greater mean ΔHR at baseline had a higher risk of adverse cardiovascular events if left untreated, and benefited from greater cardiovascular risk reduction when treated with CPAP, compared with patients with lower mean ΔHR (with adjustment for age, sex, body mass index, and cardiac intervention). The interaction analysis in their Cox regression approach using pretreatment ΔHR overcomes the healthy user bias that has affected previously published subgroup analyses that focused on *post hoc* factors such as CPAP adherence (1, 3). Here, a baseline characteristic assessed before treatment, ΔHR, was obtained in all treated and untreated patients to estimate its interaction with treatment arm (CPAP or no CPAP) on cardiovascular outcomes. Using the model, at a point estimate of ΔHR of 10 beats/min (mean + 1SD), the cardiovascular risk reduction from CPAP was 59% (95% CI, 6-82%; $P = 0.036$), whereas no significant risk reduction occurred at a lower ΔHR point estimate of 6 beats/min, which was the average ΔHR. Surprisingly, there was also a nonsignificant association of possible CPAP-related harm (hazard ratio, 1.78; 95% CI, 0.69–4.55; $P = 0.2$) in those with ΔHR < 6 beats/min.

These novel findings shed light on an important question in the sleep field: is there a subset of patients with OSA who would benefit from CPAP for secondary cardiovascular prevention? Given the neutral results from RCTs of patients with OSA and previous cardiovascular disease (CVD) (SAVE [Sleep Apnea Cardiovascular Endpoints study] [3], ISAACC [(CPAP in Patients with Acute Coronary Syndrome and OSA)] [4], and RICCADSA [1]), the theme of refuting the "one-size-fits-all" approach for treating nonsleepy or minimally sleepy patients with OSA and preexisting CVD has been recurring (5). With the recent emphasis on phenotyping and endotyping of OSA-related traits (6, 7), the field is moving toward a personalized treatment approach, with the need to identify patient subgroups at heightened risk for cardiovascular sequelae. The pulse rate response to apneas and hypopneas described previously by Azarbarzin and colleagues using SHHS (Sleep Heart Health Study) cohort data (8) does precisely that; it was demonstrated that high and low ΔHR subgroups (vs. midrange) were associated with increased risk of all-cause and CVD mortality. The present article by Azarbarzin and colleagues in this issue of the *Journal* takes the aforementioned work a step further by assessing how ΔHR modifies the effect of CPAP on cardiovascular outcomes. ΔHR, as estimated from the pulse rate derived from a pulse oximetry sensor, captures the mean difference between the lowest heart rate (HR) during a respiratory event and the highest HR after the event in a subject-specific search window (2, 8). In OSA, parasympathetic and sympathetic control of the HR is unstable, with a greater parasympathetic effect during apneas and hypopneas, thereby reducing the HR, and a heightened sympathetic tone after events, which accentuates the HR, with an overall greater ΔHR with each event (9–11). Greater ΔHR is associated with increased event severity, including degree of desaturation, arousal intensity, and longer event duration (8), all of which are characteristics of OSA that are potentially reversible by CPAP. Interestingly, CPAP had even stronger effects when ΔHR was adjusted for event severity, suggesting that underlying mechanisms involving OSA-related autonomic dysfunction are important (12). However, the precise mechanisms explaining these findings require further exploration.

The harm associated with CPAP in individuals with lower ΔHR in this study was intriguing, but caution is needed to avoid overinterpretation of this finding. If real, one possible reason for the CPAP-related harm mentioned by the authors is the elimination of hypoxic preconditioning (13) with CPAP. Another aspect that may be at play is OSA-related chronotropic incompetence, which is defined as an inability to increase the HR during exercise (14). CPAP enhances vagal tone and may further contribute to parasympathetic hyperactivity associated with chronotropic incompetence in individuals with low ΔHR, but that remains to be determined. Alternatively, as mentioned in the prior study by Azarbarzin and colleagues, low ΔHR may reflect other cardiovascular factors unrelated to OSA (8), which are less likely to be modified by CPAP treatment.

Although this study is highly informative, it is not without its limitations. As the primary analysis is continuous with the assumption of a linear relationship, determination of a threshold effect is not possible. Thus, selecting a ΔHR "cutoff" at which CPAP would be most beneficial or potentially harmful for future trials and clinical practice cannot be clearly identified using these data. However, the mean ΔHR for the group with elevated ΔHR responses (>6 beats/min) was ∼10 beats/min, and a clear benefit for this group was demonstrated. Other points of consideration that are not reported in this study were the potential importance of HR recovery after an event (15) as a marker of impaired autonomic nervous system activity and the impact of smoking and caffeine on HR responses. The impact of β-blockers on ΔHR may be relevant, but adjusting for it in this study did not affect the interaction. Nonetheless, with 89% of the study population on β-blockers and a relatively small sample size, generalizability of these findings to other populations, such as for primary cardiovascular prevention, is limited.

In summary, Azarbarzin and colleagues' findings are a welcome contribution to the OSA and cardiovascular literature, in which heterogeneity of a treatment response is a novel addition to accumulating evidence on CVD risk on the basis of subgroups identified using clinical and polysomnographic features. This work has real potential for developing enrichment strategies for future clinical trials to demonstrate the effectiveness of CPAP for OSA. Furthermore, studies evaluating the mechanisms and contributions of the autonomic nervous system to altered pulse rate responses in sleepy and nonsleepy patients with OSA before and after CPAP therapy are urgently needed for targeted interventions. ■

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Be the Change: Advancing Lung Health and Closing the Global Healthcare Gap

"I alone cannot change the world, but I can cast a stone across the waters to create many ripples."

—Mother Teresa

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Chronic respiratory disease is the leading cause of disability and death globally, and the figures are truly staggering:

- Asthma affects more than 350 million people and is the most prevalent chronic illness of childhood worldwide.
- Mild to moderate chronic obstructive pulmonary disease afflicts approximately 200 million and claims the lives of 3.2 million each year, making it the third leading cause of death globally.
- Acute lower respiratory infections account for approximately 2.4 million deaths annually.
- Lung cancer claims the lives of nearly 2 million people each year, making it the leading cause of cancer-related deaths (1).
- Approximately 1.5 million tuberculosis-related deaths occur each year (2).

And millions more live with debilitating respiratory illnesses such as sleep-disordered breathing and occupational lung disease. Furthermore, respiratory-related health issues have been exacerbated