Understanding Sleep Apnea Physiology: A Potential Path to Improving Positive Airway Pressure Effectiveness

Poor adherence to positive airway pressure (PAP) remains a barrier to effective obstructive sleep apnea (OSA) treatment for millions of patients worldwide (1, 2). To overcome this barrier, we need a firm understanding of the factors that prevent adherence and how to address them. Prior work demonstrates several key drivers of nonadherence, including racial disparities, side effects, and poor self-efficacy (3–5). For self-efficacy, our understanding has guided successful and scalable behavioral interventions (1, 6). However, our understanding of nonadherence remains incomplete, and additional targets of future intervention remain. Recent interest has focused on the role of physiologic traits in mediating nonadherence.

Rigorous work highlights that a number of distinct physiological traits contribute to OSA, with each trait varying considerably across individuals (7). These traits include loop gain, arousal threshold, pharyngeal collapsibility, and muscle compensation. Among these traits, the relationship between arousal threshold and PAP adherence has been studied in depth, with proxies of arousal threshold predicting adherence in some, but not all, cohorts (8–10). Recent work also suggests the role of elevated response of the pharyngeal dilator muscles (11). However, prior work did not fully account for each of these traits and their interactions or for changes in PAP adherence over time.

In this issue of the *Journal*, Zinchuk and colleagues (pp. 703–712) present important findings that overcome these limitations and underscore the importance of physiologic traits in predicting PAP adherence (12). Greater understanding in this area may inform novel approaches to improve the effectiveness of PAP therapy. The researchers resourcefully analyzed physiologic traits on baseline polysomnograms acquired from the RICCADSA (Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA) study. Specifically, trait values for loop gain, arousal threshold, collapsibility, and muscle compensation were calculated across non-REM sleep. The association of median trait values to objective adherence data was then evaluated in participants who used autotitrating PAP for up to 2 years ($n = 249$).

In adjusted analyses, the investigators found that lower arousal threshold, as well as high and low muscle compensation, was associated with lower adherence. A model that included baseline trait measures demonstrated utility in predicting poor adherence (defined as lowest quartile of adherence): accuracy = 69.8%, sensitivity = 38.7%, specificity = 80.2%, positive predictive value = 39.3%, and negative predictive value = 79.8%. Illustrating the clinical importance of baseline physiologic traits, the actual adherence between predicted "poor" and "good" adherers showed 2.0 and 3.2 hours/night difference at 1 month and 2 years, respectively.

The authors considered several potentially relevant covariates related to PAP adherence in their modeling strategy. These covariates included demographics, polysomnogram findings, sleepiness, medical conditions, and psychiatric conditions. However, this study was limited. As a secondary analysis, it was not comprehensive in the assessment of important factors that may confound, modify, or mediate the relationship, including symptoms, side effects, psychological factors, socioeconomic status, and partner support. Furthermore, the composition of the sample, predominantly males with cardiovascular disease, limits the generalizability of the authors' findings. These limitations highlight the need for prospective studies intentionally designed to evaluate the relationship between physiologic traits and PAP adherence in a broad population.

Elucidating the relationship between physiologic traits and PAP adherence unlocks opportunities to improve PAP effectiveness through personalization of care. First, although behavioral interventions to support adherence are effective, they are often resource intensive with limited reach (1). Identification of individuals who are likely to be nonadherent can help prioritize early access to these treatments. Second, understanding the physiologic drivers of disease may allow tailored therapies that modify physiologic traits. For instance, hypnotics have inconsistently improved adherence in randomized trials (13). Perhaps targeting individuals with low arousal thresholds could more consistently lead to meaningful improvements in adherence and symptoms. Indeed, a recent *post hoc* analysis of a randomized trial of eszopiclone suggests that those with a low arousal threshold who use PAP >1 month may derive more benefit from the hypnotic than those with a high arousal threshold (9). Several existing therapies such as acetazolamide and supplemental oxygen also have efficacy in alleviating loop gain (14), which Zinchuk and colleagues found may be a barrier in longer-term adherence (12). An underexplored approach is customizing PAP technology and settings to harmonize with physiologic traits. Although existing modes and features such as pressure ramping, fixed-pressure PAP, autotitration, bilevel PAP, adaptive servo ventilation, and expiratory pressure relief are not known to improve adherence broadly in patients with OSA (1), perhaps existing or novel PAP modes could lead to improved outcomes in individuals with specific trait profiles.

Future work will ultimately need to clarify the impact of trait identification and personalized management on patient-centered outcomes. As we innovate, we must also bear in mind the costs of complexity. The polysomnograms currently necessary for comprehensive trait identification are costly and often inaccessible, particularly for groups with existing barriers to adherence such as historically disadvantaged populations and those who live in rural areas (1, 3, 4). Developing automated approaches to measure

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traits with home testing would be an important step to mitigating this obstacle (15). Even then, additional unanticipated burdens to the health system from added complexity in decision-making and care pathways are likely. Ultimately, to reduce the burden of untreated OSA, it will be incumbent on us to integrate personalized strategies in a way that promotes equitable access to high-quality OSA care. ■

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References

1. Bakker JP, Weaver TE, Parthasarathy S, Aloia MS. Adherence to CPAP: what should we be aiming for, and how can we get there? *Chest* 2019; 155:1272–1287.
2. Drager LF, Malhotra A, Yan Y, Pépin JL, Armitstead JP, Woehrle H, *et al.*; medXcloud group. Adherence with positive airway pressure therapy for obstructive sleep apnea in developing vs. developed countries: a big data study. *J Clin Sleep Med* 2021;17:703–709.
3. Wallace DM, Shafazand S, Aloia MS, Wohlgemuth WK. The association of age, insomnia, and self-efficacy with continuous positive airway pressure adherence in black, white, and Hispanic U.S. veterans. *J Clin Sleep Med* 2013;9:885–895.
4. Billings ME, Cohen RT, Baldwin CM, Johnson DA, Palen BN, Parthasarathy S, *et al.* Disparities in sleep health and potential intervention models: a focused review. *Chest* 2021;159:1232–1240.
5. Chai-Coetzer CL, Luo Y-M, Antic NA, Zhang XL, Chen BY, He QY, *et al.* Predictors of long-term adherence to continuous positive airway pressure therapy in patients with obstructive sleep apnea and cardiovascular disease in the SAVE study. *Sleep (Basel)* 2013;36: 1929–1937.
6. Sparrow D, Aloia M, Demolles DA, Gottlieb DJ. A telemedicine intervention to improve adherence to continuous positive airway pressure: a randomised controlled trial. *Thorax* 2010;65:1061–1066.
7. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *Am J Respir Crit Care Med* 2013;188:996–1004.
8. Zinchuk A, Edwards BA, Jeon S, Koo BB, Concato J, Sands S, *et al.* Prevalence, associated clinical features, and impact on continuous positive airway pressure use of a low respiratory arousal threshold among male United States veterans with obstructive sleep apnea. *J Clin Sleep Med* 2018;14:809–817.
9. Schmickl CN, Lettieri CJ, Orr JE, DeYoung P, Edwards BA, Owens RL, *et al.* The arousal threshold as a drug target to improve continuous positive airway pressure adherence: secondary analysis of a randomized trial. *Am J Respir Crit Care Med* 2020;202:1592–1595.
10. El-Solh AA, Lawson Y, Wilding GE. Impact of low arousal threshold on treatment of obstructive sleep apnea in patients with post-traumatic stress disorder. *Sleep Breath* 2021;25:597–604.
11. Zinchuk AV, Redeker NS, Chu J-H, Liang J, Stepnowsky C, Brandt CA, *et al.* Physiological traits and adherence to obstructive sleep apnea treatment in patients with stroke. *Am J Respir Crit Care Med* 2020;201:1568–1572.
12. Zinchuk AV, Chu J, Liang J, Celik Y, Op de Beeck S, Redeker NS, *et al.* Physiological traits and adherence to sleep apnea therapy in individuals with coronary artery disease. *Am J Respir Crit Care Med* 2021;204:703–712.
13. Wang D, Tang Y, Chen Y, Zhang S, Ma D, Luo Y, *et al.* The effect of non-benzodiazepine sedative hypnotics on CPAP adherence in patients with OSA: a systematic review and meta-analysis. *Sleep* [online ahead of print] 26 Mar 2021; DOI: 10.1093/sleep/zsab077.
14. Terrill PI, Edwards BA, Nemati S, Butler JP, Owens RL, Eckert DJ, *et al.* Quantifying the ventilatory control contribution to sleep apnoea using polysomnography. *Eur Respir J* 2015;45:408–418.
15. Orr JE, Sands SA, Edwards BA, Deyoung PN, Deacon N, Jen R, *et al.* Measuring loop gain via home sleep testing in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2018;197:1353–1355.

The Reductionist Conundrum of an "Updated" Definition of Extensively Drug-Resistant Tuberculosis

In September 2006, newspapers announced the arrival of "killer strains" of tuberculosis (TB). "Extensively drug-resistant tuberculosis," or "XDR-TB" as it was later known, gained notoriety following a deadly outbreak in rural KwaZulu-Natal, South Africa. Of the 53 people with the disease, 52 perished quickly (1). Most had been living with HIV, had experienced prolonged diagnostic delays and suboptimal therapeutic regimens, and had inadequate psychosocial and socioeconomic support. However, the humans and their illness experience were forgotten as the global public health community focused on one aspect—the drug susceptibility profile of the infecting organisms (2). XDR-TB came to be defined as disease caused by strains of *Mycobacterium tuberculosis* with *in vitro* resistance to isoniazid and rifampin (multidrug-resistant [MDR] TB) and to the fluoroquinolones and injectable agents, the backbone of MDR-TB treatment at the time (3).

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