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Physiology May Be the Key: Cardiovascular Risk Stratification in Obstructive Sleep Apnea

It has been 40 years since Sullivan and colleagues first described the effectiveness of continuous positive airway pressure (CPAP) therapy in obstructive sleep apnea (OSA) (1). Since then, CPAP therapy has become the most popular therapy for OSA because it ameliorates many adverse consequences of OSA. It is widely accepted that CPAP therapy reduces daytime sleepiness and risk of crashes and improves quality of life, erectile function, and systemic blood pressure (2, 3).

There has been considerable interest in the impact of OSA on cardiovascular health. Abnormal breathing in OSA is associated with several physiologic insults that are implicated in the development of cardiovascular disease (CVD), such as intermittent hypoxemia and hypercapnia, sleep fragmentation, autonomic activation (4), and large intrathoracic pressure swings that have been shown to promote inflammation, endothelial dysfunction, and metabolic derangements. Observational studies have consistently shown associations between OSA and hypertension (5), coronary disease and heart failure (6), atrial fibrillation (7), stroke (8), and CVD deaths (9). Many studies have shown that CPAP therapy improves endothelial function (10) and reduces inflammatory markers (11), blood pressure (12), and early signs of atherosclerosis (13). Together, these observations suggest that CPAP therapy should reduce the risk of CVD in patients with OSA. However, several randomized controlled trials (RCT) and meta-analyses have shown no risk reduction in CVD events from the use of CPAP therapy in OSA (14). While the validity of the RCT findings and their generalizability to clinical sleep apnea populations continues to generate considerable debate, it is fair to say that the role of CPAP therapy in CVD prevention remains uncertain.

A potential explanation for the ineffectiveness of CPAP therapy in reducing CVD events in OSA observed in RCTs is that the effect of OSA on CVD could vary between individuals. Although OSA severity is generally quantified using frequency-orientated metrics such as the apnea–hypopnea index (AHI) and oxygen desaturation index, these

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metrics may not adequately quantify the magnitude of OSA-related physiologic insults that are experienced by an individual with OSA and that could contribute to CVD events. This has led to efforts to identify OSA subgroups that appear to be most vulnerable to CVD events and efforts to stratify patients with OSA according to measurable physiologic insults. To this end, several studies have highlighted an association between the severity of OSA-related hypoxemic burden and CVD events (15).

In this issue of the *Journal*, Azarbarzin and colleagues (pp. 1546–1555) report on associations between the pulse rate response to an apnea or hypopnea (ΔHR) and CVD outcomes (16). The ΔHR, measured by pulse oximetry, is considered a biomarker of the autonomic (sympathetic and parasympathetic) response to a respiratory event and is a novel method of attempting to quantify another potentially important OSA-related physiologic insult. The authors examined the association between ΔHR and CVD in two community-based cohorts.

In a preliminary analysis of 1,395 middle-aged and older adults without overt CVD from the MESA (Multi-Ethnic Study of Atherosclerosis) cohort, the cross-sectional association between ΔHR and subclinical CVD biomarkers (coronary calcium, NT-proBNP, and Framingham risk score) was explored. The study found a U-shaped relationship between ΔHR and subclinical CVD biomarkers. Compared with those with mid-ΔHR (25th–75th centiles), individuals with high ΔHR (upper quartile) and low ΔHR (lowest quartile) had elevated biomarker scores. The authors postulate that a high ΔHR may reflect more severe respiratory events or an overreactive autonomic system, both of which are likely to adversely affect the cardiovascular system. In contrast, a low ΔHR may represent more subtle respiratory events or an underresponsive cardiovascular system, possibly owing to heart disease, diabetes, or other causes of autonomic dysfunction. This hypothesis was consistent with the observation that individuals with a low ΔHR were older and had a higher baseline pulse rate and a higher prevalence of established CVD.

In the primary analysis of 4,574 adults from the SHHS (Sleep Heart Health Study) cohort, the investigators examined the association of ΔHR with nonfatal and fatal CVD events and all-cause mortality over a mean follow up of 10.7 years. Compared with those with mid ΔHR, participants with high ΔHR had an increased risk of nonfatal and fatal CVD and all-cause mortality. The highest risk was observed in participants with high ΔHR and severe OSA as defined by the AHI and substantial hypoxemic burden, suggesting an additive effect of different physiological insults. An exploratory analysis found that the association between high ΔHR and increased risk of CVD and all-cause mortality was exclusively observed in nonsleepy individuals.

If these findings are validated in prospective studies, they imply that measurements of OSA-related physiologic insults may be more accurate prognostic markers of CVD risk than AHI and oxygen desaturation index in isolation. The measurement of ΔHR could be easily incorporated into home sleep studies, as it relies only on measurements of respiration and pulse oximetry, and analysis can be automated. The ability to identify patients with OSA at higher risk of CVD would facilitate the design of future clinical trials to assess the role of CPAP therapy on CVD events. The association of high ΔHR with CVD morbidity and mortality in individuals without excessive sleepiness may be particularly valuable in facilitating the inclusion of nonsleepy individuals with an increased CVD risk profile in future randomized trials. These findings are important steps toward developing a more sophisticated and personalized approach to managing OSA. ■

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New Diagnostics to Infer Risk in Tuberculosis
Is the Term "Latent Tuberculosis Infection" Obsolete?

Accurate diagnosis and estimation of risk in latent tuberculous infection (LTBI) remains a major clinical and global health challenge (1, 2). *Mycobacterium tuberculosis* (Mtb) infection reflects a continuum between LTBI and active tuberculosis (TB). LTBI is the most common form Mtb infection, which affects one-quarter of the world's population and kills approximately 2,000,000 people every year (3, 4). Immunocompetent individuals with LTBI have a 5–10% risk of developing active TB during their lifetime, most commonly within the first 2 years after exposure (5). Treatment of LTBI is effective in reducing the risk of developing subsequent active TB disease, but identifying patients most at risk of developing active TB and ensuring successful LTBI treatment remain significant challenges (1, 2).

Available laboratory tests for the detection of LTBI have serious diagnostic limitations, including a poor predictive value (<5%) for identifying subjects with LTBI who will actually develop active TB (1). Tuberculin skin testing and IFN-γ release assays can detect cell-mediated immune reactivity in Mtb infection. However, none of these tests can differentiate LTBI from active TB, nor can they distinguish between those who achieve subsequent bacterial clearance and/or effective infection containment from others who have silent and persistent infection at high risk to develop TB (6). Therefore, improvements in current TB diagnostics are urgently needed not only to improve both sensitivity and specificity of Mtb infection detection but also to more accurately determine the risk of progression or reactivation into active disease. Such advances in diagnostic testing could consequently improve the selection of people who would actually benefit from TB preventive therapy, thus helping to improve TB control and eradication efforts in many parts of the world (1, 2, 7).

The World Health Organization established the goal of reducing active TB and corresponding mortality by 90% and 95%, respectively, by 2035. This will be unachievable without new prevention strategies, including new diagnostic approaches for rapidly identifying infection in asymptomatic patients at the highest risk for developing active TB (1, 2, 8). Fortunately, there has been important scientific progress in recent years in our understanding of TB pathophysiology as well as in the development of new predictive diagnostics and preventive therapies (6). Among these new TB diagnostics, detection of blood RNA signatures have been validated to not only differentiate LTBI from TB but also to predict those who will likely progress to TB ("incipient TB") within 2 years (7, 9, 10). Blood-based immune profiling methods have been developed and validated to differentiate LTBI from TB, but until now, their predictive value has not been validated in adults (7, 11).

In this issue of the *Journal*, Mpande and colleagues (pp. 1556–1565) retrospectively studied antigen-specific T-cell activation markers in blood, measured with flow cytometry (FC) assays that can stratify different stages of TB infection and thus infer risk of TB progression (12). They selected a subset of available blood samples from a large prospective adolescent cohort study that were serially tested with QuantiFERON-TB Gold In-Tube (QFT) to define "recent" (QFT conversion <6 mo) and "remote" (persistent QFT+ for >1 yr) TB infection reactivity. They identified and defined the ΔHLA-DR median fluorescence intensity (MFI) biomarker as the difference in HLA-DR expression between IFN-γ+ TNF+ Mtb-specific and total CD3+ T cells (12, 13). The diagnostic performance of this composite FC biomarker was assessed by blinded prediction in test cohorts with "recent" versus "remote" TB infection reactivity. They also applied a single-cell TCR sequencing to measure the ΔHLA-DR MFI biomarker results and conducted an unblinded analysis of asymptomatic individuals with LTBI who remained healthy (nonprogressors) or who progressed to microbiologically confirmed TB disease (progressors) from a separate cohort of the same adolescent study. In the test cohorts, frequencies of Mtb-specific T cells differentiated between QFT(−) and QFT(+) individuals (area under the curve [AUC] of the receiver operating characteristic curve and 95% confidence intervals: 0.94; 0.87–1.00). ΔHLA-DR significantly differentiates between "recent" and "remote" individuals with TB infection reactivity (0.91; 0.83–1.00), "remote" TB infection reactivity and newly diagnosed TB (0.99; 0.96–1.00), and TB progressors and nonprogressors (0.75; 0.63–0.87). The authors conclude that the ΔHLA-DR biomarker can identify individuals with recent Mtb infection and those with disease progression, allowing targeted provision of preventive treatment to those at highest risk of TB (12).

We applaud the authors for this important research work with high significance for global TB control. The study was retrospective but reasonably well-designed and utilized stored blood samples from a large prospective cohort study for their training, testing, and validation study

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