ultimately included these ethical principles in the Commonwealth's framework to allocate scarce COVID-19 therapeutics during the pandemic (7). ■

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Can Pulse Rate Responses Be a Metric of Cardiovascular Outcome in Patients with Obstructive Sleep Apnea?

To the Editor:

The effect of apnea- and hypopnea-related changes in pulse rate on cardiovascular morbidity and mortality was investigated by Azarbarzin and colleagues (1) in a secondary analysis of the Multi-Ethnic Study of Atherosclerosis (n = 1,395) and the Sleep Heart Health Study (n = 4,575). First, I would like to congratulate the team on their study, emphasizing the importance of heart rate as a physiological and prognostic metric beyond the apnea–hypopnea index. In their study, the authors used three distinct types of apnea–hypopnea heart rate (HR)–related changes: "high ΔHR (upper quartile), mid-ΔHR (25th–75th centiles), and low ΔHR (lower quartile)." The authors defined ΔHR as the difference between the maximum and minimum pulse rate during apneas/hypopneas. They found that the upper quartile of pulse rate changes was associated with increased cardiovascular morbidity and mortality risk. The main findings of the study corroborate our previous work on the WSCS (Wisconsin Sleep Cohort Study) using actual electrocardiogram-derived signal (R-R interval tracing) (2). However, the WSCS secondary analysis excluded individuals on chronotropic medications (e.g., a β-blocker or calcium channel blocker), which dampen the autonomic response to respiratory events and affect the sensitivity of the heart rate metric (3). It is plausible that the lower ΔHR quartile represents a group of individuals on chronotropic medications, explaining the U shape relationship between pulse rate and adverse cardiovascular outcome. Azarbarzin and colleagues added the β-blockers' use to the adjusted model, but perhaps a separate analysis for those on β-blockers versus those not on them could provide additional useful mechanistic information. The mechanism of increased incidence of cardiovascular disease (CVD) and association with heart rate changes can be explained by an increased sympathetic tone and shear forces leading to endothelial dysfunction (4).

These pathophysiological factors are greatly influenced by demographics variables, particularly age and sex. However, this study did not provide information about the sex and age effect on cardiovascular morbidity and mortality. In WSCS, we found that increased heart rate changes were significantly associated with new-onset CVD event(s) in men but not in women.

On the basis of the findings from three different cohorts, it is essential to start considering heart rate response frequency during a sleep study as an important physiological metric and predictor of cardiovascular outcome in patients with obstructive sleep apnea. Therefore, future prospective studies are greatly needed to avoid any potential bias and to confirm these novel findings that could have a paradigm shift in the field. ■

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Sleep Apnea, Pulse Rate Response, and Cardiovascular Events with Special Reference to Biomarkers

To the Editor:

Azarbarzin and colleagues evaluated the association between the pulse rate response to apneas/hypopneas (ΔHR) and cardiovascular disease (CVD) morbidity/mortality (1). The authors used three subclinical CVD biomarkers, namely, coronary artery calcium, N-terminal probrain natriuretic peptide (NT-proBNP), and Framingham risk score, to assess their associations with ΔHR, and U-shaped relationships were exclusively observed. In addition, individuals with obstructive sleep apnea with elevated ΔHR had increased risks of CVD morbidity/mortality. They concluded that the three biomarkers for obstructive sleep apnea were effective for risk stratification of CVD morbidity/mortality. However, I have a query regarding some discrepancies for the risk of CVD morbidity/mortality in patients with low and high ΔHR.

There is an agreement that obesity has an inverse relationship with NT-proBNP (2); however, the progression of apnea/hypopnea cancels the inverse relationship between body mass index (BMI) and NT-proBNP (3). Azarbarzin and colleagues included individuals with mild-to-moderate sleep apnea, and the average BMI was less than 29 (1). I speculate that there is an inverse relationship between BMI and NT-proBNP in this population and that BMI may become a confounding factor in the relationship between ΔHR and CVD morbidity/mortality. Thus, I recommend an additional setting of low ΔHR as a control to compare the risk of CVD morbidity/mortality between patients with low and high ΔHR. ■

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Reply to Sankari and to Kawada

From the Authors:

We thank Dr. Abdulghani Sankari and Dr. Tomoyuki Kawada for their interest in our work published recently in the *Journal* (1). In our recent study (1), we found a U-shaped relationship between the pulse rate response to sleep apnea (ΔHR) and subclinical cardiovascular biomarkers as well as nonfatal and fatal cardiovascular events. That is, a low ΔHR and a high ΔHR appear to be deleterious. In addition, in our previous studies, we have shown that the ΔHR reflected the severity of preceding respiratory events (2) and the intensity of cortical arousal (3) and was reproducible (4) and heritable (5). Here, we clarify questions raised by Dr. Sankari and Dr. Kawada.

Dr. Sankari wrote to suggest that adjustment for β-blocker use may not adequately deal with a confounding effect of β-blockers on the association between the ΔHR and cardiovascular disease (CVD) outcomes. Indeed, in addition to adding β-blocker use in the main models, we conducted a sensitivity analysis and excluded individuals receiving β-blockers, those with the presence of atrial fibrillation, or those with cardiac pacemakers. The results remained very similar (1). In addition, Dr. Sankari asked about age- and sex-specific associations. The sex-specific associations were included in our study (1) and showed that the associations between a high ΔHR and nonfatal CVD or fatal CVD appeared to be stronger in women than in men (but interactions were not statistically significant). In new, age-specific analyses (age ⩾65 vs. <65 yr), associations also appeared to be

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