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Reply to: Heart Rate Response in Obstructive Sleep Apnea: A Clue to Reveal Cardiovascular Benefit from Continuous Positive Airway Pressure?

To the Editor:

We thank Huang and colleagues for their interest in our article by Azarbarzin et al. published recently in the *American Journal of Respiratory Critical Care Medicine* (1). In this study (1), we found that a higher pulse rate response to respiratory events ([ΔHR]) was an effect modifier of the treatment benefit of the continuous positive airway pressure (CPAP). Here, we clarify questions raised by Huang and colleagues (2).

Huang and colleagues (2) wrote about the utility of hypoxic burden as an effect modifier of CPAP benefit. We emphasize that our previous analysis (3), involving ΔHR and hypoxic burden predicting cardiovascular (CV) risk, was complicated by its observational nature: We used high hypoxic burden to define the presence versus absence of obstructive sleep apnea (OSA). We found that high ΔHR in those with OSA (defined by high hypoxic burden as >62% min/h) was strongly associated with adverse CV outcomes in the Sleep Heart Health Study (3). Importantly, the reference group for this finding was mid-ΔHR. Although low ΔHR was also associated with adverse outcomes in some analyses, we did not reason that low ΔHR was an OSA-related hazard; that is, mechanistically, we considered that low ΔHR was a measure of a non–OSA-related CV hazard (3), such as less severe respiratory events (4) or an underresponsive cardiovascular system, possibly caused by existing heart disease (5), long-standing diabetes (6), or other causes of autonomic dysfunction. We proposed that large, frequent surges in heart rate contribute causally to OSA-related CV consequences and could be ameliorated with OSA treatment; a low "heart rate burden" in those with low ΔHR would not provide such a therapeutic opportunity.

The analysis of CPAP treatment benefit is far simpler. In the RICCADSA (Randomized Intervention with CPAP in CAD and Sleep Apnea) trial, we asked whether higher ΔHR was an effect modifier of the treatment benefit of CPAP. Hypoxic burden was not part of the definition of OSA here; the definition of OSA was already decided as part of the RICCADSA inclusion criteria. We started from the notion that patients had sufficient OSA for us to assess whether ΔHR is important. In this reply, on the basis of our preliminary findings, we share an additional finding from the RICCADSA trial that higher hypoxic burden was not associated with CPAP treatment benefit. There were also no indications of a three-way interaction between hypoxic burden, ΔHR, and CPAP treatment. Thus, ΔHR alone appeared to have the most prognostic value. We caution that the study has limited power to identify three-way interactions.

We share the concerns about pulse rate and heart rate signals in the face of various arrhythmias. Pulse rate was considered the most translatable signal (i.e., could be obtained from home oximetry), which is a major goal of our work, and our prior studies had established pulse rate as an informative signal for ΔHR analysis. ECG-derived heart rate, when filtered at about 6 seconds (moving time median), closely matched the pulse rate signal by visual inspection in the current patient cohort. Numerous example signals were inspected, and only four patients with chronic atrial fibrillation appeared to provide pulse rate data that we believed differed meaningfully from the ECG-based measures. Excluding these four individuals did not change our findings (1).

Finally, we agree wholeheartedly that we are just beginning to quantify how OSA affects the autonomic nervous system as a means to identify those who may benefit most from OSA therapy. However, as other investigators join this line of inquiry and

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propose new measures, we encourage them to ensure that their measures meaningfully capture OSA-specific risk and test whether treating OSA confers benefit in one group over another. We hope that, together, as a field, we will develop sound inclusion criteria for future CPAP trials, selecting patients whose physiologic data reveals high risk of adverse CV outcomes in OSA. ■

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Microbial Burden-associated Cytokine Storm May Explain Nonresolving Acute Respiratory Distress Syndrome in Patients with COVID-19

To the Editor:

We read with great interest the article reported by Kullberg and colleagues in the *Journal* on the association of lung microbiota of critically ill patients with coronavirus disease (COVID-19) with nonresolving acute respiratory distress syndrome (ARDS) (1). The study enrolled patients with COVID-19 under mechanical ventilation, and the primary clinical outcome was successful liberation from mechanical ventilation on Day 60 after starting mechanical ventilation (1). The authors showed that successfully extubated patients with COVID-19 have significantly less alveolar microbial burden in the lower respiratory tract and significantly less mortality than deceased or intubated patients on Day 60 after initiation of mechanical ventilation (1, 2). Unfortunately, how the enhanced microbial burden affected the clinical outcome of patients with COVID-19 remains unclear. Several studies have documented the importance of increased systemic and intraalveolar concentrations of inflammatory cytokines in the pathogenesis of COVID-19 or sepsis-associated ARDS (3–5). Thus, the significant correlation observed by the authors between the microbial burden and the bronchoalveolar lavage fluid concentration of inflammatory cytokines points to intraalveolar cytokines as the potential factors mediating the detrimental effects of enhanced microbial burden in patients with COVID-19 with ARDS. However, Kullberg and colleagues assessed correlations in all (extubated and deceased or intubated) patients and in all (first and followed-up) BAL fluid samples. The two groups were not separately evaluated. In addition, the difference in the BAL fluid concentrations of inflammatory cytokines between the two groups of patients was not evaluated. Therefore, it is difficult to determine whether inflammatory cytokines played some pathogenic role in the (deceased or intubated) group of patients with COVID-19 with poorer clinical outcomes.

To clarify the potential implication of excessive cytokine secretion as the process mediating the pathological effects of the enhanced lung bacterial or fungal burden in patients with COVID-19 with nonresolving ARDS, the BAL fluid concentrations of inflammatory cytokines and the strength of correlation of microbial burden with inflammatory cytokines should be separately evaluated and compared between the extubated and deceased or intubated groups. Addressing the above questions will provide important and original information on whether increased lung microbial burden–associated "cytokine storm" may explain nonresolving ARDS in critically ill patients with COVID-19. ■

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