Reply to Goligher *et al.*: Physiology Is Vital to Precision Medicine in Acute Respiratory Distress Syndrome and Sepsis

From the Authors:

We thank Goligher and colleagues for their insightful comments on our recent research statement highlighting the need to incorporate physiology in ongoing and future precision medicine studies for sepsis and the acute respiratory distress syndrome (ARDS) (1). We completely agree that the inclusion of physiologic variables and physiologic responses is necessary and in our research statement had intended them to be considered under the broader category of "clinical" biomarkers. Currently, the variables or combination of variables that contribute to heterogeneity of treatment effect in sepsis and ARDS are unknown, and we agree that excluding any domain of variables is potentially harmful. We appreciate the opportunity to clarify and expand the discussion.

Physiologic variables and physiologic responses do indeed have a proven track record of informing heterogeneity of treatment effect in pulmonary and critical care as exemplified by distribution of emphysema and ventilatory parameters for lung volume reduction surgery and endobronchial coils in chronic obstructive pulmonary disease, lung elastance for ARDS ventilation, or markers of fluid responsiveness in sepsis (2–5). Physiologic variables may both explain and predict response to treatment with several advantages for precision medicine strategies. First, as suggested by Goligher and colleagues, physiologic responses can potentially inform whether a patient is benefitting from or being harmed by a therapy in a manner that is more rapid than a biochemical assay. Second, physiologic variables may be measured more readily across a variety of geographic and socioeconomic settings than with other variables; thus, precision medicine strategies incorporating physiology may be more easily deployed when molecular assays or complex computational approaches are not feasible.

We respectfully add that the caveats addressed in our research statement must apply to physiologic variables. Similar rigor is required for the inclusion of physiologic variables in precision medicine for sepsis and ARDS as is necessary for other domains such as biochemical assays. Consensus definitions and standardized protocols for the measurement of physiologic variables should be used to ensure reproducibility and to facilitate validation of findings, and conscious efforts should be made to harmonize physiologic data in sepsis and ARDS knowledge networks. Evidence that change in a physiologic measure impacts patient-centered outcomes is vital. Importantly, as addressed by Goligher and colleagues, findings suggesting heterogeneity of treatment effect based on physiologic variables, no matter how intuitive, must still be confirmed in prospective clinical trials. In this regard, ongoing trials testing driving pressure for ARDS are exemplars of translating computational approaches suggesting heterogeneity of treatment effect to advance precision medicine (6–8).

We similarly agree that combinations of data from multiple domains are likely to inform precision medicine moving forward. The variables determining heterogeneity of treatment effect may not be limited to molecular, clinical, or physiologic variables alone, reinforcing the need to remain inclusive. Indeed, we believe that the knowledge networks necessary to detect and explain why patients are or are not responding to treatment will require all types of data, and assessment for interactions between them, to advance precision medicine for sepsis and ARDS. ■

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Faraaz Ali Shah, M.D., M.P.H.
University of Pittsburgh
Pittsburgh, Pennsylvania

and

Veterans Affairs Pittsburgh Healthcare System
Pittsburgh, Pennsylvania

Nuala Meyer, M.D., M.S.
University of Pennsylvania
Philadelphia, Pennsylvania

Derek C. Angus, M.D., M.P.H.
University of Pittsburgh
Pittsburgh, Pennsylvania

Sachin Yende, M.D., M.Sc.*
University of Pittsburgh
Pittsburgh, Pennsylvania

and

Veterans Affairs Pittsburgh Healthcare System
Pittsburgh, Pennsylvania

ORCID ID: 0000-0002-6596-8034 (S.Y.).

*Corresponding author (e-mail: yendes@upmc.edu).

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Mild Intermittent Hypoxia: A New Treatment Approach for Patients with Obstructive Sleep Apnea and Hypertension

To the Editor:

With interest, we read the paper of Panza and colleagues (1), which confirms mild intermittent hypoxia (MIH) elicits beneficial cardiovascular and autonomic outcomes in males with obstructive sleep apnea (OSA) and concurrent hypertension. OSA causes a series of brief, severe episodes of hypoxia and hypercapnia, leading to persistent, maladaptive chemoreflex-mediated activation of the sympathetic nervous system, ultimately leading to hypertension. Conversely, substantial evidence in animals and humans suggests that a controlled intermittent hypoxia conditioning program is a safe and effective way to prevent and treat hypertension (2). The results of this study and previous studies (3) provide a solid theoretical basis for exploring the long-term treatment of MIH and determining the most effective dose, which is very important for the treatment of OSA with cardiovascular disease.

Sustained increases in motor neuron, nerve, and muscle activity that contribute to ventilation and maintain upper airway patency are evident after intermittent exposure to stimulation. This sustained increase is known as long-term facilitation and is the principal form of respiratory plasticity that has been documented in humans (4). Early research found mild forms of experimentally induced intermittent hypoxia might be cardiovascular, neurocognitive, and metabolically protective (5). In addition to lowering blood pressure, intermittent hypoxia may also trigger many other beneficial cardiovascular effects. Repeated daily exposure to intermittent normal and hypobaric pressures in rats reduces myocardial infarct size, protects the heart from subsequent infarcts, increases left ventricular contractility, and improves overall cardiac function (6). Given the financial healthcare burden associated with these OSA-related cardiovascular diseases, MIH as a treatment modality represents a viable, low-cost strategy with high therapeutic benefit in a manner that ensures safety and efficacy. Applying MIH therapy during waking hours is more convenient for patients and staff. In general, we do not recommend applying MIH during sleep, as stimulation may cause sleep disruption and a series of sleep-deprived complications.

On the basis of the above evidence, we believe that MIH may be used in the future for the treatment of OSA-related cardiovascular disease, but there are practical issues with receiving MIH, including dose, duration of exposure (which requires further research), and equipment requirements. Therefore, further studies are needed to determine the ideal interplay between hypoxia intensity, episode duration, regimen length, and exposure days leading to an optimal MIH response. Selection of an appropriate dose, characterized by the frequency, duration, and intensity of exposure, will depend heavily on the correct identification of a range of biomarkers (7). In terms of equipment, we think to design a mouth–nose mask with a switch, and then set a certain time to close for 10–60 seconds (the time can be adjusted), so that MIH treatment can be performed by simulating the airway obstruction of patients with OSA.

On the basis of the above viewpoints, although the sample size of this study is small, Panza and colleagues (1) showed that MIH can be used as a new treatment method to improve cardiovascular complications in patients with OSA. It is worth looking forward to the long-term efficacy study of MIH treatment in multicenter and large sample sizes. ■

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Riken Chen, M.D.*
Dongxing Zhao, M.D.*
The First Affiliated Hospital of Guangzhou Medical University
Guangzhou, Guangdong, China

State Key Laboratory of Respiratory Disease
Guangzhou, Guangdong, China

Guangzhou Institute of Respiratory Disease
Guangzhou, Guangdong, China

and

National Clinical Research Center for Respiratory Disease
Guangzhou, Guangdong, China

Qinglan Wu, M.D.*
Central People's Hospital of Zhanjiang
Zhanjiang, Guangdong, China

Xiaojuan Chen, M.S.*
Medical College of Jiaying University
Meizhou, Guangdong, China

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