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Reply to Chen *et al.*

From the Authors:

We would like to thank Chen and colleagues for their commentary on our recently accepted manuscript (1). The authors cited published literature that outlined the theoretical support and current mechanisms linked to the therapeutic effects of mild intermittent hypoxia (2). However, the current understanding of the use of mild intermittent hypoxia as a therapeutic modality is scant, as many studies report findings that would not be considered therapeutic (2). The reason for this discrepancy is that much of the intermittent hypoxia literature is focused on understanding the pathophysiological impact of severe intermittent hypoxia in an effort to better understand the negative impact of obstructive sleep apnea (2, 3).

Chen and colleagues, in their response to our manuscript, highlighted long-term facilitation, the principal form of respiratory plasticity initiated by intermittent hypoxia. Subsequently, Chen and colleagues cited evidence of positive clinical outcomes associated with mild intermittent hypoxia. However, many of these positive clinical outcomes are impacted by notable heterogeneity in the intermittent hypoxia protocols used, as well as various patient populations (2). Thus, a more detailed understanding of the hypoxia protocols used is required to use this intervention therapeutically.

The impact of carbon dioxide when combined with mild intermittent hypoxia warrants consideration when exploring the positive outcomes of this therapy. Published findings indicate that carbon dioxide should be maintained at or slightly above baseline concentrations during administration of intermittent hypoxia to elicit long-term facilitation of ventilation in humans. Likewise, the maintenance of carbon dioxide at isocapnic concentrations may be necessary for long-term facilitation of upper airway muscle activity, as our study (*see* the online supplement) showed that upper airway function was modified following exposure to mild intermittent hypoxia. On the other hand, the maintenance of carbon dioxide concentrations may not be required if autonomic and cardiovascular outcomes are of primary interest. We address this issue because this is an important distinction that was not discussed in the commentary by Chen and colleagues.

Although mild intermittent hypoxia may provide therapeutic benefit, we have previously reported that administering intermittent hypoxia with sustained mild hypercapnia immediately before sleep can increase disease severity in those with sleep apnea (4). The mechanism associated with this increase is likely owing to an increase in loop gain during sleep (5), which is further impacted by inflammation (6) and the time of day (7). Thus, the time that mild intermittent hypoxia is administered is a crucial step in understanding the therapeutic potential of this intervention. We suggest that administration of mild intermittent hypoxia

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many hours before sleep onset may mitigate the detrimental effects that increases in loop gain have on apnea severity. However, further work is required to determine if other forms of plasticity (long-term facilitation of upper airway muscles) that could mitigate apnea will be ineffective if administered many hours before sleep.

Another issue not addressed in the commentary is the need to maintain a consistent dose of mild intermittent hypoxia. The inability to maintain a consistent dose within or across days of therapy will clearly lead to inconsistent outcome measures. In our study, we tightly regulated the partial pressure of end-tidal oxygen and consequently oxygen desaturation by blending in 100% oxygen during the hypoxic exposures (average oxygen desaturation = 88.14% $\pm$ 0.69%). This consistency is not attainable if an individual inhales from an air source with a lower fractional concentration of oxygen or 100% nitrogen without the administration of supplemental oxygen. If uncontrolled, oxygen saturation will vary between episodes and often will decline beyond the intended target of mild oxygen desaturation. This is an important consideration for clinical application, as the inability to control the intensity of the hypoxic exposure will expose patients to highly varying degrees of oxygen desaturation. The uncontrolled desaturation to severe oxygen desaturation could lead to negative clinical outcomes. Thus, we caution against using a protocol with a fixed hypoxic duration when degrees of oxygen desaturation cannot be consistently maintained.

Overall, we appreciate the commentary and support from Chen and colleagues. We believe the issues the authors addressed are practical and will be solved in time. Ultimately, solving these issues will lead to larger multisite clinical trials to gauge the therapeutic effectiveness of mild intermittent hypoxia. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Clinical Implications of Obstructive Sleep Apnea Diagnostic Misclassification

To the Editor:

We have read with interest the study recently published in the *Journal* by Lechat and colleagues (1), which highlights the significant variability in the results obtained from consecutive sleep studies for OSA diagnosis and severity. According to the conclusions of this study, up to 20% of patients are misclassified in terms of their severity of OSA (on the basis of the apnea–hypopnea index [AHI]) if they only undergo a sleep study during 1 single night (the most common clinical practice). Although there are some other studies on this topic, even a recent meta-analysis (2, 3), it is really necessary to congratulate the authors for the effort made in their study to analyze an average of 170 consecutive sleep tests in more than 67,000 individuals.

However, we think it is very important to answer two additional questions to assess the extent to which these results have a relevant clinical impact and can help clinicians to better manage their patients from both a diagnostic and therapeutic viewpoint.

On the one hand, we have to assume that the cutoff points in the AHI usually used to classify the severity of OSA are, to a certain extent, arbitrary, as the impact of OSA or the need for continuous positive airway pressure (CPAP) treatment depends not only on the AHI value but also on other circumstances, such as the patient's clinical characteristics or the outcome analyzed (4). Apart from the misclassification of patients owing to sleep test variability based on

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