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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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Jiangpeng Lin, M.D.*
Donghao Wang, 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

Mingdi Chen, M.D.*
The Second Affiliated Hospital of Guangdong Medical University
Zhanjiang, Guangdong, China

Junyan Lin, 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

Zhenzhen Zheng, M.D.‡
The Second Affiliated Hospital of Guangdong Medical University
Zhanjiang, Guangdong, China

ORCID ID: 0000-0001-6101-7891 (R.C.).

*These authors contributed equally to this work.
‡Corresponding author (e-mail: zhengzhenzhen2018@163.com).

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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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