The effect of intermittent hypoxia on obstructive sleep apnea: beneficial or detrimental?

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OBSTRUCTIVE SLEEP APNEA (OSA) is a significant public health problem owing to both prevalence and debilitating long-term negative consequences. OSA typically occurs in individuals whose narrow upper airways (UA) make them dependent on UA dilator muscle tone to maintain UA patency. In these patients the reduction in UA muscle activity that takes place during sleep results in UA collapse, apnea, hypoxemia/hypercapnia, and subsequent arousal. Increases in UA resistance at sleep onset cause reflex activation of UA muscles (4). If this compensatory response is sufficient, as it is for most people, breathing stabilizes, albeit at a higher level of CO2 than during wakefulness. If insufficient, the resulting blood gas changes and attempts to breathe against an occluded UA will produce arousal. Thus, in people with mild OSA, even a slight improvement in muscle responsiveness may reduce the number and frequencies of UA collapse-induced arousals/awakenings.

Another potentially compensatory mechanism in OSA is long-term facilitation (LTF), a process whereby exposure to acute intermittent hypoxia (AIH) or repeated carotid sinus nerve stimulation causes a persistent increase in respiratory activity. As the most extensively studied form of respiratory plasticity, LTF has been investigated for three decades, but its physiological significance is still unclear. Recently, however, investigators have begun to appreciate its potential clinical implications in OSA. In rats, LTF is more easily induced during sleep vs. wakefulness (15). In humans that are healthy (8) or suffer from sleep apnea (10), LTF cannot be elicited under normocapnic conditions during wakefulness but is evident when CO2 levels are modestly elevated (8). LTF is also elicited during sleep in OSA patients (1) (see 12 for review). In addition, it appears that AIH preferentially induces LTF in UA dilating muscle vs. pump muscle activity during sleep, as AIH induces LTF in genioglossal activity (6), UA conductance (1), and ventilation (2) without concomitant pump muscle LTF. In rats, pretreatment with chronic intermittent hypoxia (CIH) enhances AIH-induced LTF and the hypoxic ventilatory response (HVR) (11). CIH also increases the CO2 reserve (the difference between the CO2-apneic threshold and the resting equilibrium value) in dogs (9). These data suggest that AIH and CIH are beneficial factors.

It should be noted, however, that whether LTF is beneficial or even plays any role in OSA is still uncertain. OSA symptoms worsen as the night progresses, inconsistent with LTF being a beneficial factor. OSA symptoms also get worse over time in many patients, inconsistent with CIH being a beneficial factor, although some other risk factors (e.g., obesity, aging, and excessive reactive oxygen species), which accumulate over time, may also contribute to this worsening trend. It has been postulated that repeated hypocapnia between OSA events might inhibit LTF expression in OSA patients (12). However, it should be noted that hypercapnia will always occur concomitant with hypoxia during OSA events, and LTF, if elicited, is quite resilient to various disturbances in rats (13), although recent findings suggest it may be impacted by sleep deprivation/sleep fragmentation (14).

There are two sides of the HVR coin, too. On one hand, increases in the HVR will increase UA dilating muscle activity, thus decreasing UA resistance (3). On the other hand, an enhanced HVR may increase the respiratory control system loop gain, which will cause destabilization of UA and respiration. Spontaneous fluctuations in ventilation during sleep can contribute to UA collapse. UA muscle activity parallels the level of ventilation as it waxes and wanes and UA collapse may occur during nadirs. Exaggerated HVR will produce an undershoot of arterial CO2, leading subsequently to hypventilation and concomitant reduction of UA dilator muscle activity, thereby increasing the likelihood of another collapse. Thus a high HVR is thought by many to destabilize breathing in OSA.

For these reasons a clear understanding of factors that affect HVR and LTF in OSA patients is very much needed. However, much of what we know of control of breathing, and virtually all that we know about CIH, has come from animal studies. It is uncertain whether those findings are applicable to humans. To really understand how HVR, LTF, and CIH affect OSA, it is necessary to study OSA patients.

In this issue of the Journal of Applied Physiology, Gerst et al. (7) describe a study of untreated moderate OSA patients, in which HVR and ventilatory LTF (vLTF) were measured in the morning and evening, before and after repeated daily (10 days) exposure to AIH (i.e., CIH). They found that both HVR and AIH-induced vLTF were augmented after CIH. Both of them also exhibited diurnal fluctuations, i.e., HVR was greater and vLTF was smaller in the morning vs. evening. If exaggerated HVR is detrimental and LTF is beneficial, these two diurnal fluctuations may jointly contribute to the worsening trend of OSA symptoms during the night, as postulated by the authors. Nevertheless, gradual increases during the night in rapid-eye-movement (REM) sleep time (5), arousal threshold (17), and/or sleep fragmentation (16) may also contribute to the worsening trend. To our knowledge, this is the first identification of an LTF-enhancing effect of CIH in humans. The findings that CIH enhances HVR and vLTF confirm the previous animal studies and suggest that these two mechanisms are not saturated by the OSA-produced nocturnal hypoxic episodes and that the magnitude of LTF can be enlarged by certain forms of CIH in those moderate OSA patients.

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These findings lay the foundation for further studies to define the clinical significance of these manipulations and to explore the potential therapeutic treatment for OSA. A strength of the study is that it was conducted on patients with mild-to-moderate OSA, the very group most likely to benefit from treatment. The study of Gerst et al. (7) has some limitations. The experimental conditions were different from those during spontaneous UA obstructions. For example, end-tidal CO2 (PETCO2) was raised 3 mmHg above the eupneic level [although this could also be considered a strength as this technique to facilitate LTF induction with raised PETCO2 is rather novel (8)].

The hypoxic episodes in the AIH (also CIH) protocol were also unnatural. In addition, HVR and vLTF measurements were conducted during wakefulness, not sleep when OSA events occur, and the possible influence of nocturnal exposure to intermittent hypoxia was unclear.

Gerst et al. (7) have taken an important step in addressing the title question of this editorial article. However, many basic questions remain unanswered: Does LTF occur naturally in OSA patients? Does LTF play an important role in OSA? Which subgroups of patients can benefit from manipulations of LTF or HVR? And so on. Ultimately the effects of LTF and HVR changes may be complicated, varying between patients and even within patients across the night or as their disease progresses. Therefore, there is still a lot to learn about HVR, LTF, and CIH effects on OSA.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES