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# Hypoxia and Sleep-disordered Breathing
## Friend or Foe?

Hypoxia is a hallmark feature of respiratory disease and has multiple effects on the central nervous system. For example, experimentally induced acute sustained isocapnic hypoxia (oxygen saturation as measured by pulse oximetry [$Sp_{O_2}$], 80–85%) blunts respiratory sensation (1) and symptom perception in asthma (2) and suppresses cough reflex sensitivity (3) and arousal responses to airway closure during sleep in healthy individuals (4). The effects of repetitive intermittent hypoxia, as occurs nightly in sleep-disordered breathing, are generally considered deleterious for the cardiovascular system. For instance, 2–4 weeks of nightly intermittent hypoxia increases daytime blood pressure and sympathetic nerve activity in healthy individuals (5, 6), potentially via renin-angiotensin mechanisms (7). In addition, the overnight sleep apnea–related hypoxic burden metric, which includes both hypoxemia frequency and magnitude components, predicts cardiovascular mortality (8–10).

However, as highlighted in this issue of the *Journal* in the current proof-of-concept physiology study conducted in a group of hypertensive men with obstructive sleep apnea (OSA) by Panza and colleagues (pp. 949–958) (11) and by others (12, 13), not all aspects of hypoxemia are necessarily deleterious. The rationale for the current study was based largely on the authors' prior work that investigated specific hypercapnic intermittent hypoxia regimes and the subsequent facilitatory effects on respiratory and upper airway neurons (14, 15) and the work of others that indicates that mild intermittent hypoxia during wakefulness can reduce blood pressure via nitric oxide mechanisms in untreated hypertensive patients in whom OSA status is unknown (16). The three key study findings were that intermittent hypoxia



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led to *1*) improved upper airway stability during sleep assessed via critical collapsing pressure measurements; *2*) greater continuous positive airway pressure (CPAP) adherence; and *3*) an ∼10 mm Hg reduction in systolic and diastolic blood pressure during quiet wakefulness and sleep per 24-hour blood pressure measurements.

The study protocol involved a randomized parallel-arm design in which people with OSA were studied at the onset of their CPAP treatment. Participants were allocated to an adjunct intervention of intermittent hypoxia ($n = 10$ completed) or sham ($n = 6$ completed) in addition to their nightly CPAP therapy. The intervention involved administration of 2 minutes of 8% inspired oxygen (leading to reductions in $Sp_{O_2}$ of ∼85–88%) with mild hypercapnia, every 2 minutes for 40 minutes during wakefulness, applied each weekday for 3 weeks. As acknowledged by the investigators, some of the study limitations include the small sample size, yet larger samples, given the intensive interventions, would be challenging; the absence of women and the racial background of the study participants (17), which may impact generalizability; and a relatively large proportion of dropouts (36%), although a secondary intention-to-treat analysis confirmed the reported per-protocol effects. Although largely focused on physiology mechanisms, this study (NCT03736382) also serves as a reminder of the need to clearly articulate study outcomes *a priori* when registering our randomized trials online.

Notwithstanding, the current findings of increased upper airway stability during sleep and increased CPAP compliance after targeted intermittent hypoxia are consistent with earlier respiratory stimulatory findings (14, 18). Also, in accordance with the current findings, ischemic preconditioning mechanisms may provide cardiovascular benefit in certain settings (19, 20), including potentially in certain people with OSA (21–23). Indeed, further highlighting the potential benefit of intermittent hypoxia, recent *post hoc* analyses of randomized trials of CPAP to treat OSA have raised the possibility that amelioration of OSA in certain patient subgroups (i.e., moderately severe OSA in the SAVE [Sleep Apnea Cardiovascular Endpoints] trial [24], low heart rate responses in the RICCADSA [Randomized Intervention with Continuous Positive Airway Pressure in Coronary Artery Disease and OSA] trial [25]) might even be deleterious for cardiovascular health.

Although the findings from the current (11) technically challenging detailed human physiology experiments, for which the authors are to be commended, are intriguing and add to the knowledge on this interesting topic, many important unresolved questions remain. First, how can the current decreased blood pressure findings be reconciled with previous contrasting experimentally induced intermittent hypoxia data in humans that used similar hypoxia magnitudes (5–7)? Oxygen desaturation by ∼10% every 4 minutes would provide an equivalent "hypoxic burden" of ∼150% min/h for the 40-minute intervention period. If the equivalent intensity of hypoxemia occurred nightly during sleep, this intervention would place patients in the highest risk category for cardiovascular morbidity and mortality based on analysis of Azarbarzin and colleagues (8). Perhaps the "mild" nature of the intermittent hypoxia in the current study is related more to the relatively short duration of cumulative exposure (40 min/d vs. 6 h [7] or overnight [5, 6] in prior studies) and, thus, an equivalent hypoxic burden of just 12.5% min/h if the remaining 8 hours were hypoxia free (i.e., very low risk category per Azarbarzin and colleagues [8]). To date, however, a U-shaped curve that describes the potential benefit of hypoxia at the mild end and harm at the other is yet to be demonstrated. Indeed, observational data have linked even milder intermittent hypoxia (in OSA) with cardiovascular morbidity and hypertension (26, 27), and interventional data have also not shown elevated blood pressure with amelioration of OSA-induced hypoxemia (28, 29). Time-of-day effects (i.e., daytime vs. nighttime exposure) may also be important (30, 31). Thus, it remains unknown whether the observed benefits are contingent on daytime administration and the absence of sleep disruption.

In addition to questions on optimal dose and cumulative exposure, which are clearly crucial (12), understanding which subgroups or phenotypes of patients may experience benefit versus harm from targeted intermittent hypoxia interventions and the various perpetuating factors (Figure 1) will be important. For example, individuals with large heart rate (sympathetic) responses to respiratory events appear to be at greatest cardiovascular risk of OSA-related hypoxemia (25, 32). It is possible that such individuals may experience more harm than benefit.

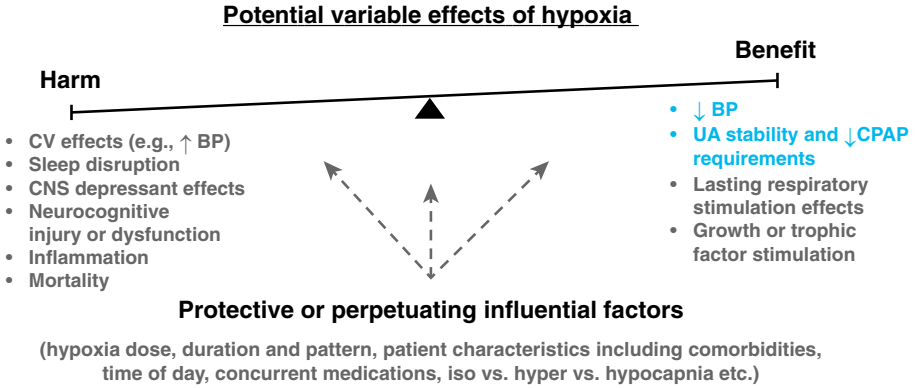


**Figure 1.** Seesaw diagram outlining some of the potential differential effects of hypoxia in humans and examples of the various protective or perpetuating factors that may influence the balance between harm and benefit. Current study findings are highlighted in blue. BP = blood pressure; CNS = central nervous system; CPAP = continuous positive airway pressure; CV = cardiovascular; UA = upper airway.

Finally, whether the current observations reflect transient compensatory responses or are long lasting is unknown. Similarly, the precise underlying mechanisms (endocrine or neurophysiological) that mediate reductions in blood pressure with intermittent hypoxia require further investigation. Indeed, given that daily intermittent hypoxia regimes are not likely to be clinically feasible as a therapeutic option, to maximize the potential "friend" and minimize the "foe" impacts (Figure 1), mechanistic knowledge to determine if specific beneficial components can be feasibly targeted with nonhypoxia interventions will be important for future clinical translation. ■

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