Intermittent hypoxia: a low-risk research tool with therapeutic value in humans

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Mateika JH, El-Chami M, Shaheen D, Ivers B. Intermittent hypoxia: a low-risk research tool with therapeutic value in humans. J Appl Physiol 118: 520–532, 2015. First published December 30, 2014; doi:10.1152/japplphysiol.00564.2014.—Intermittent hypoxia has generally been perceived as a high-risk stimulus, particularly in the field of sleep medicine, because it is thought to initiate detrimental cardiovascular, respiratory, cognitive, and metabolic outcomes. In contrast, the link between intermittent hypoxia and beneficial outcomes has received less attention, perhaps because it is not universally understood that outcome measures following exposure to intermittent hypoxia may be linked to the administered dose. The present review is designed to emphasize the less recognized beneficial outcomes associated with intermittent hypoxia. The review will consider the role intermittent hypoxia has in cardiovascular and autonomic adaptations, respiratory motor plasticity, and cognitive function. Each section will highlight the literature that contributed to the belief that intermittent hypoxia leads primarily to detrimental outcomes. The second segment of each section will consider the possible risks associated with experimentally rather than naturally induced intermittent hypoxia. Finally, the body of literature indicating that intermittent hypoxia initiates primarily beneficial outcomes will be considered. The overarching theme of the review is that the use of intermittent hypoxia in research investigations, coupled with reasonable safeguards, should be encouraged because of the potential benefits linked to the administration of a variety of low-risk intermittent hypoxia protocols.

Humans; sleep apnea; cardiovascular and autonomic function; respiratory plasticity; cognitive function

RESEARCH IN THE MATEIKA LABORATORY over the past 20 yr focused on the relationship between intermittent hypoxia and the initiation of respiratory plasticity in animals (65, 101) including intact humans (63, 91, 103, 113, 159), humans with sleep-disordered breathing (81, 91) and, more recently, humans with spinal cord injury (150, 152). Over this period of time, a number of studies targeted toward the field of sleep-disordered breathing have led to the view that intermittent hypoxia is the principal, if not the only, risk factor for the development of a number of detrimental cardiovascular, respiratory, metabolic, and cognitive outcomes [see (8, 24, 58, 71) for reviews on this topic]. Consequently, other risk factors, including intermittent hypercapnia, intermittent airway closing, and arousal from sleep have received less attention as potential risk factors. More importantly, for this review, the protocols that were employed to establish the link between intermittent hypoxia and detrimental outcomes were typically severe in regards to intensity, duration, or both. Thus the role that pattern, intensity, and duration of application have on physiological outcome measures was largely ignored and the beneficial effects linked to milder forms of intermittent hypoxia were generally overlooked.

The following review is designed to highlight the intermittent hypoxia protocols that initiate beneficial physiological responses. Generally speaking, the intermittent hypoxia protocols considered in this review that meet this criteria are defined by episodes of mild hypoxia (e.g., 10–14% oxygen) that are short in duration (e.g., 15 s to 4 min), small in number (e.g., 10 episodes), and have a short length of exposure (e.g., 1 h or less), although these milder protocols may also have some inherent risks (see INTERMITTENT HYPOXIA - MOTOR PLASTICITY, DETRIMENTAL OUTCOMES). When appropriate, more severe protocols that are not linked to detrimental outcomes are also addressed. Details regarding specific differences between protocols can be found in a previously published review (105). Each section of the review is divided into three parts. The first part of each section highlights the literature that contributed to the belief that intermittent hypoxia leads primarily to detrimental outcomes. Studies related to sleep apnea will be considered primarily, because a hallmark of this disorder is intermittent hypoxia and there is concern within the community that this stimulus is responsible for a variety of detrimental outcomes. Although the detrimental effects of severe intermittent hypoxia on a variety of physiological outcomes have been established

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in animal models and in some human phenotypes, we will address findings that suggest the role of intermittent hypoxia in initiating harmful outcomes (in some patients with sleep apnea) is less significant than initially portrayed. The second part of each section will consider intervention studies that employ experimentally rather than naturally induced intermittent hypoxia. The outcomes in these studies will be examined for the possible risk-to-benefit ratio of experimentally induced intermittent hypoxia. Finally, the body of literature that indicates that intermittent hypoxia initiates primarily beneficial outcomes will be considered. In addressing the literature the effect of intermittent hypoxia on cardiovascular, respiratory, and cognitive adaptations will be highlighted and human studies will be emphasized. The overarching theme of the review is that the use of intermittent hypoxia in research investigations, coupled with reasonable safeguards, should be encouraged because of the potential benefits linked to the administration of a variety of low-risk, intermittent hypoxia protocols. In contrast, intermittent hypoxia should not be considered unsafe simply on the basis of the term alone.

**INTERMITTENT HYPOXIA - CARDIOVASCULAR AND AUTONOMIC ADAPTATIONS**

**Detrimental Outcomes**

Fletcher and colleagues initially showed in rats that exposure to severe intermittent hypoxia (i.e., 12 s infusions of nitrogen every 30 s, 7 h/day for 35 days) was accompanied by dramatic and sustained increases in blood pressure (i.e., 10–14 mmHg) (34–37, 40). Additional studies in rats also showed that less severe protocols (e.g., 5% oxygen leading to an oxygen saturation of 70% for 7–8 h/day over 14 days), but severe nonetheless, were also associated with increases in blood pressure (4, 77, 99). These studies also demonstrated that the elevations in blood pressure were linked to chronic increases in sympathetic nervous system activity (34, 39) that were a consequence of augmented afferent activity originating from the carotid bodies in response to intermittent hypoxia (38). These findings were the impetus to investigate the effect of intermittent hypoxia on autonomic and cardiovascular function in humans with sleep apnea.

The first line of evidence indicating a possible link between intermittent hypoxia and blood pressure in humans were epidemiological studies that reported that blood pressure increases were linked to apnea severity, or the percentage of time below 90% oxygen saturation, or both (66, 100, 119, 123, 144, 166, 167). Findings from these studies can be viewed in a similar manner to results derived from computer modeling because the nature of the findings from both categories of studies serve as a guide to experimentally explore the possible mechanisms responsible for an identified physiological problem, but they do not identify cause-and-effect relationships. Consequently, the findings obtained from epidemiological studies may not be evident once the hypothesis is tested experimentally. Indeed, if increases in blood pressure are directly associated with nighttime exposure to intermittent hypoxia the effect may be small in some patients (67). In support of this notion, Hoffstein and Mateika reported that blood pressure in the morning (i.e., immediately upon awakening) compared with measures in the evening (i.e., obtained prior to onset of sleep) were not different in patients with mild to moderate sleep apnea (67). Moreover, although morning blood pressure measures were significantly elevated in patients with severe sleep apnea the effect was small (i.e., 2 mmHg) (67). More importantly, when the patients with sleep apnea were matched to a control group on the basis of age and body mass index no differences were observed (67). In line with these observations, a recent meta-analysis of published findings revealed that elimination of intermittent hypoxia with continuous positive airway pressure, compared with sham continuous positive airway pressure or treatment with placebo tablets, led to significant but small reductions in systolic (2.2 ± 0.7 mmHg) and diastolic (1.9 ± 0.7 mmHg) blood pressure during wakefulness (32). The findings from this meta-analysis reflect a quantitative analysis of pooled data from other studies that reported similar reductions, or unaltered measures, in blood pressure (12, 61, 111, 139) in patients with mild to moderate sleep apnea. It may be contended that the small reductions in blood pressure reflect short treatment periods and suboptimal adherence to treatment or issues related to study design. However, blood pressure reductions in select studies with longer treatment periods and adequate adherence, or studies that employed experimental designs graded as intermediate or high quality were not associated with greater reductions in blood pressure. This was particularly evident in patients with mild to moderate sleep apnea. Thus hypoxemia may contribute to increases in blood pressure; however, the effect may be small or absent in the case of mild to moderate hypoxemia and diminished in some severe cases (32, 67). The emerging postulation from recent studies is that the greatest benefit of treatment with continuous positive airway pressure on blood pressure is most clearly evident in a subgroup of patients with uncontrolled, resistant hypertension (10, 68), which may be unrelated to the severity of sleep apnea (10).

Investigators have hypothesized that the link between intermittent hypoxia and blood pressure in humans is via increased sympathetic nervous system activity induced by enhanced peripheral chemoreflex sensitivity to hypoxia (78, 121, 122, 163). The findings typically highlighted are that sympathetic nervous system activity is increased in individuals with sleep apnea (16, 26, 118) and that this increase is accompanied by enhanced peripheral chemoreflex sensitivity to hypoxia (118). Moreover, treatment with nasal continuous positive airway pressure to eliminate exposure to intermittent hypoxia for a specified length of time (i.e., 6 to 12 mo) decreases levels of muscle sympathetic nervous system activity during wakefulness (70, 117, 161). Consequently, many clinicians are under the impression that there is a direct link between intermittent hypoxia, enhanced sympathetic nervous system activity, and hypertension.

However, published results suggest that the links between these variables are fragile. Normotensive blood pressure measurements are evident in patients with sleep apnea independent of levels of muscle sympathetic nerve activity under baseline conditions and following treatment with continuous positive airway pressure (117). In addition, resting muscle sympathetic activity has been reported to be greater in patients with sleep apnea compared with control participants, however, this increase does not consistently manifest itself in blood pressure measurements, which are similar in control participants and those with sleep apnea during wakefulness (11, 78). It might be maintained that the elevation in sympathetic nervous system
activity is an early marker of subsequent increases in blood pressure. If this is the case, elevated levels in muscle sympathetic nervous system activity might be expected in hypertensive compared with normotensive patients with sleep apnea. However, Carlson et al. reported that elevated levels of muscle sympathetic nervous system activity were similar in normotensive and hypertensive patients with sleep apnea (16). This finding suggests that measures of sympathetic activity in patients with sleep apnea may not be linked to blood pressure. The alternative explanation could be that increases in sympathetic activity are responsible for initiating but not maintaining sustained increases in blood pressure. If so, additional experimental studies in humans are required to substantiate this speculation. Carlson et al. also reported that resting muscle sympathetic activity was not correlated with disease severity expressed as either apnea frequency or minimum nocturnal oxygen saturation (16). This latter finding implies that other physiological mechanisms may have an equal or greater effect on sympathetic nervous system activity and blood pressure. Limited experimental studies in humans indicate that nighttime increases in autonomic nervous system activity and blood pressure occurs in humans who experience increases in upper airway resistance (i.e., snoring) accompanied by significant intrathoracic pressure swings (50, 102), and in response to arousal from non-rapid eye movement sleep without accompanying hypoxemia (49, 84, 128, 129). Thus the elimination of upper airway resistance, intrathoracic pressure swings, and arousal following treatment with continuous positive airway pressure could account for the decreases in blood pressure that have been documented. In support of this speculation, a recent randomized clinical trial showed that treatment with continuous positive airway pressure resulted in a reduction of mean arterial pressure of −2.8 mmHg relative to a control group. In contrast, no changes in blood pressure were evident in a group of patients with sleep apnea who were treated with nocturnal supplemental oxygen (55). Likewise, treatment of sleep apnea with continuous positive airway pressure resulted in reductions in excessive daytime sleepiness and muscle sympathetic nervous system activity that were strongly correlated (28).

The relationship between intermittent hypoxia and blood pressure may be linked through other mechanisms. These include dysfunction of vasoconstrictor (e.g., endothelin) and vasodilator (e.g., nitric oxide) endothelial factors, abnormalities in the renin-angiotensin-aldosterone system, or circulating levels of atrial natriuretic peptide (79, 85, 86, 125). This speculation is directly supported by results that revealed that vascular responses (reactive hyperemic blood flow and forearm vascular conductance) likely impaired by local vasodilator mechanisms (69, 74, 80) responded to treatment with continuous positive airway pressure despite blood pressure measures that were unresponsive to treatment (69). In contrast, no experimental studies in humans with sleep apnea have established a direct link between intermittent hypoxia and blood pressure via the atrial natriuretic peptide or renin-angiotensin system-dependent mechanism, although this link is supported by studies completed in rats and mice (19, 48, 83, 88, 114).

In summary, nocturnal intermittent hypoxia may be a contributing factor to increases in muscle sympathetic nervous system activity and cardiovascular dysfunction; however, the effect may be absent in the case of mild and moderate hypoxemia (Fig. 1). Likewise, absent or minimal cardiovascular dysfunction in some individuals who experience severe intermittent hypoxia is also evident (Fig. 1), and studies to determine the reasons for this absence would be of interest. Furthermore, equal emphasis on other physiological mechanisms (e.g., arousal and intrathoracic pressure swings) with an equal or greater effect on cardiovascular function will serve to move the field forward.

Evidence of Low-Risk Outcomes

Independent of the degree to which nightly exposure to hypoxemia affects blood pressure in individuals with sleep apnea, there has been concern in recent years that acute (i.e., one-time exposure), experimentally induced intermittent hypoxia, whether severe, moderate, or mild, has a significant detrimental effect on autonomic and cardiovascular function. If so, this would ultimately prevent intermittent hypoxia from being used as an experimental tool to examine the role of this stimulus as a treatment modality or in initiating physiological adaptive changes. A number of studies have investigated sympathetic nervous system and blood pressure responses following exposure to brief episodes of intermittent hypoxia in healthy young adults over a 20- to 30-min period (22, 92, 93, 112, 148). In some cases, intermittent hypoxia was coupled with simulated apneic events (22, 92, 93, 112). Exposure to this type of protocol elicited increases in muscle sympathetic nerve burst activity in most (22, 92, 93, 112) but not all studies (148). However, the relevance of this increase is difficult to interpret because increases in muscle sympathetic activity were either not accompanied by increases in blood pressure (i.e., systolic, diastolic, and mean arterial pressure) and heart rate (22), or the increases were small (i.e., 2–3 mmHg) (92, 93) and, in some cases, sustained for only short time periods (i.e., 5 min) (92). Cutler and colleagues also reported that forearm blood flow, forearm vascular resistance, stroke volume, cardiac output, and total peripheral resistance remained unchanged following exposure to intermittent hypoxia despite an observed increase in muscle sympathetic nerve activity (22). Similarly, Tamisier and colleagues reported no significant changes in blood pressure, forearm blood flow, heart rate, or muscle sympathetic nervous system activity following a 2-h exposure to 30–40 episodes/h of hypoxia (i.e., average oxygen saturation 92%) (148).

Healthy humans have also been repeatedly exposed to intermittent hypoxia on a daily basis over a 10- to 30-day period. In contrast to acute exposure, these longer exposures could potentially lead to profound and sustained elevations in sympathetic nervous system activity and blood pressure. However, the preponderance of evidence indicates that this is typically not the case, particularly for protocols of mild to moderate intensity. Those studies that exposed healthy participants to relatively brief, intermittent hypoxia protocols (i.e., 6–12 cycles of intermittent hypoxia with each cycle 5 min in duration) each day for 12 days reported no changes in resting blood pressure (3, 42, 96) or measures of autonomic function (i.e., heart rate variability) (42) from the initial to final days of the protocol. In contrast, the findings from more prolonged exposures are less consistent. A daily 6-h exposure to hypoxic episodes of short duration for 4 days reportedly led to a baseline increase in diastolic and mean arterial pressure (4 mmHg) when the initial to the final days of the protocol were
compared (41). However, on each day prior to the administration of intermittent hypoxia, acute responses to hypoxia were measured. Baseline measures of diastolic and systolic pressure prior to the measurement of acute responses to hypoxia were similar on the initial and final day of the protocol (41). The reasons for the discrepant baseline measures (i.e., baseline measures prior to acute testing vs. before exposure to intermittent hypoxia) were not addressed. A more severe protocol in which healthy participants were exposed to intermittent hypoxia for 9 h/day for 28 days did not elicit increases in heart rate and systolic blood pressure after 28 days of exposure (52). Likewise, diastolic blood pressure did not increase after 14 days, but an increase of 3 mmHg was evident after 28 days (52). The increase in diastolic pressure was accompanied by increases in muscle sympathetic nervous system activity in five of seven participants along with forearm vascular resistance (52). However, these two variables were not correlated. In a subsequent investigation, this same group of investigators using a similar protocol reported that a 5 mmHg increase in diastolic blood pressure was evident in healthy individuals following 1 day of exposure to intermittent hypoxia (149). In addition to the discrepant findings, the result was thought-provoking because an additional 13 days of exposure did not lead to further increases in diastolic blood pressure (149). Furthermore, increases in blood pressure were evident only during the day and did not manifest during exposure to intermittent hypoxia over the 8-h period of sleep. The reason for the day-night differences could not be explained. Likewise, the role of intermittent hypoxia in the daytime elevations of blood pressure was not substantiated because of the absence of a control group. Nevertheless, independent of the stimulus responsible for the elevation in blood pressure, this measure returned to baseline values after 5 days of recovery (149). Recovery may have occurred earlier, but these measures were not obtained.

Collectively, the results suggest that 1 to 2 h of exposure to mild episodes of hypoxia acutely or repeatedly for 10–110 days does not lead to sustained changes in autonomic or cardiovascular function and, consequently, the risk associated with this exposure is minimal (Fig. 1). Longer exposures (i.e., 6–8 h/day) for more than 2 wk may lead to sustained increases in blood pressure (Fig. 1). However, the reported increase in diastolic
pressure is not uniform, since Fu and colleagues reported that exposure to hypoxia 3 h/day for 4 wk was not accompanied by changes in mean arterial pressure, heart rate, cardiac output, or total peripheral resistance (43). Finally, even if small increases in blood pressure (e.g., 2–3 mmHg) are sustained for short periods following longer exposures to intermittent hypoxia, the return to baseline occurs quickly, and thus severe exposures have not been linked to sustained adverse outcomes in healthy, normotensive participants (Fig. 1).

Despite the absence of profound alterations in blood pressure in healthy participants following repeated daily exposure to mild intermittent hypoxia, concern remains that a similar exposure might result in dangerous consequences in participants whose health is compromised. This issue may be of particular relevance to individuals with multiple comorbidities such as diabetes and heart disease. Additional studies are required to establish the risk level and potential benefits of mild exposure to these populations. In the meantime, Trumbower and colleagues showed in patients with spinal cord injury that repeated daily exposure to intermittent hypoxia (15 × 1.5-min episodes of 9% oxygen) was not accompanied by increases in systolic and diastolic blood pressure after exposure on a given day or after 5 days of exposure to the protocol (64, 153). Likewise, we found that repeated daily exposure to 12 × 4-min episodes of hypoxia (50 mmHg, 87% oxygen saturation) over a 10-day period was not accompanied by increases in blood pressure or changes in heart rate variability (i.e., a noninvasive measure of sympathetic and parasympathetic nervous system activity) from the initial to the final days of the protocol (51).

Therefore, there is evidence to suggest that administration of short protocols employing mild forms of intermittent hypoxia (in regards to both duration and intensity of hypoxic exposure) pose a minimum risk to autonomic or cardiovascular function in healthy humans, or humans with compromised health (Fig. 1) (for additional discussion on this topic see intermittent hypoxia - cardiovascular and autonomic adaptations, Beneficial Outcomes).

Beneficial Outcomes

Contrary to popular dogma, there is evidence that administration of intermittent hypoxia is beneficial to cardiovascular function (141). To avoid repetition we refer readers to the review by Serebrovskaya and colleagues titled “Intermittent hypoxia: cause of or therapy for systemic hypertension” for details (141). The review cites [see Table 1 in (141)] a number of studies completed in the former Soviet Union that revealed that exposure to only a few episodes of hypoxia for a short duration of time each day for 10 to 30 days resulted in profound decreases in blood pressure (e.g., a decrease of 10–30 mmHg in systolic and 10–15 mmHg in diastolic blood pressure) in individuals with hypertension (141). The reported decreases in blood pressure were significantly reduced compared with values reported following treatment with continuous positive airway pressure in individuals with sleep apnea (141). Appropriate controls are required in future studies to confirm the results of the investigations outlined in the review by Serebrovskaya and colleagues (141). An intriguing hypothesis is to explain the role of intermittent hypoxia in reducing blood pressure in individuals with hypertension [see Fig. 2 in (141)] was proposed. Briefly, Serebrovskaya and colleagues (141) suggested that mild forms of intermittent hypoxia produce reactive oxygen species that function as signaling molecules that are essential to induce beneficial cerebrovascular and cardiovascular adaptations. These adaptations include cytoprotective antioxidant enzyme activities in erythrocytes, liver, heart, and brain. These authors also propose that exposure to mild forms of intermittent hypoxia 1) stimulates endothelium-dependent relaxation and prevents endothelial dysfunction, as previously observed in hypertensive rats, and 2) promotes formation of nitric oxide stores that contribute to adaptive responses of the circulation and protects against damaging effects of excessive nitric oxide synthesized during prolonged repeated exposure to hypoxia and decreased production of nitric oxide by endothelial cells.

Thus less severe hypoxic protocols than those initially used in rat studies may have a beneficial effect on the cardiovascular system (Fig. 1). Interestingly, preliminary work in mice has shown that 24 h of exposure to moderate forms of hypoxia results in profound decreases in blood pressure over a 72-h recovery period (5), although further studies utilizing a pattern of intermittent hypoxia is necessary because sustained hypoxia was employed. Besides reducing blood pressure, intermittent hypoxia may also initiate a host of other beneficial cardiovascular effects. For example, short periods of intermittent hypoxia in rats induces ischemic preconditioning, which protects the heart from subsequent infarction, whereas repeated daily exposure to intermittent hypoxia in healthy lean mice (115) and mice with heart failure (116) leads to increased left ventricular contractility and improves overall cardiac function. One of the more intriguing findings in the literature uncovered enhanced coronary collateral vessel development in individuals with obstructive sleep apnea (146). It has been postulated that this angiogenesis may be initiated by the release of vascular endothelial growth factor in response to nocturnal intermittent hypoxia (11, 146).

In summary, published data indicate that intermittent hypoxia protocols that are moderate in intensity and duration do not pose a significant cardiovascular risk to humans (Fig. 1). Indeed, in many instances intermittent hypoxia may ultimately prove to be an effective therapeutic option in some individuals suffering from cardiovascular disease. Additional well-designed human experimental studies are required to further support this hypothesis.

INTERMITTENT HYPOXIA - MOTOR PLASTICITY

Detrimental Outcomes

Naturally or experimentally induced hypoxia might also be considered precarious because a number of studies in rats have reported that exposure to chronic, intermittent hypoxia leads to reductions in hypoglossal nerve activity or to detrimental alterations in contractile properties or muscle fiber distribution (27, 30, 95, 145, 157, 160). These detrimental outcomes were initiated by daily exposure to protocols consisting of 20 to 60 hypoxic episodes per hour over 8–12 h per day over 3–9 wk (27, 30, 95, 145, 157, 160). The intensity of hypoxia ranged from 0 to 9% (27, 30, 95, 145, 157, 160). Thus detrimental outcomes in upper airway muscle function have generally been associated with prolonged exposure to intermittent hypoxia that was severe. To our knowledge, these types of protocols...
have not been employed in humans, so it remains unclear whether similar outcomes would be initiated.

Intermittent hypoxia might also be considered precarious because recent studies from the Mateika laboratory indicate that this stimulus increases chemoreflex sensitivity to hypoxia (51, 81, 103, 113, 159) and the promotion of apneic events (165) (Fig. 1). Detailed information that addresses the link between chemoreflex sensitivity and apneic events can be found in previous review articles from the Mateika laboratory (104, 106). Briefly, ventilation increases after arousal from an apneic event in part because of feedback from the peripheral chemoreceptors responding to the accompanying hypoxia and hypercapnia. This increase in ventilation is required to restore blood gas values to homeostatic levels. However, repeated exposure to intermittent hypoxia enhances chemoreflex sensitivity (51, 81, 103, 113, 159), which could result in an inappropriately high level of ventilation after arousal from an apneic event. The enhanced response could cause a reduction in carbon dioxide that could lead to the cessation of the breathing rhythm to motoneurons that innervate both chest wall and upper airway muscles upon return to sleep (104). Thus a gradual enhancement of chemoreflex sensitivity may ultimately exacerbate breathing instability (104, 106). This possibility is supported by small clinical investigations that have reported that the frequency (31, 142) and duration (15, 18, 142) of breathing events increases from the evening to the morning in individuals with sleep apnea. Likewise, we showed that acute exposure to intermittent hypoxia in the presence of hypocapnia is accompanied by an increase in the number of apneic episodes (165). Thus short exposures to mild forms of intermittent hypoxia may initiate breathing instability during sleep (Fig. 1).

**Beneficial Outcomes**

Despite this possible side effect, intermittent hypoxia also promotes forms of plasticity that may contribute to mitigating apnea or treating sleep apnea more efficiently (104, 106) and is known to effectively promote recovery of respiratory (151) and motor limb function (64, 153) (Fig. 1).

The role that intermittent hypoxia has in promoting upper airway patency has received support from animal and human studies. Acute exposure to intermittent hypoxia enhances hypoglossal nerve and genioglossus muscle activity (13, 20, 44, 45, 63, 101, 110) in humans and animals. The magnitude of this response is further enhanced by repeated daily exposure to intermittent hypoxia (168). The cellular components and pathways responsible for this form of plasticity are gradually being revealed (9). A comparison of the protocols that result in reductions in upper airway muscle function and those that initiate beneficial increases indicates that hypoxic intensity may be coupled to different outcomes. However, independent of intensity, both the episode duration (e.g., 90 s vs. 5 min) and the duration of repeated exposure (e.g., 1 wk vs. 5 wk) may also play a significant role in determining the final outcome. For example, despite a similar hypoxic intensity (9% vs. 11%) and overall exposure length per day (i.e., total exposure to hypoxia of 6 h/day), reductions in hypoglossal nerve activity were reported in one study (157) compared with enhanced responses in other studies (168). Shorter episodes (90 s vs. 5 min) coupled to a daily exposure that lasted for a longer duration (3 wk vs. 1 wk) was linked to reductions in hypoglossal nerve activity (157, 168). Consequently, further studies are required to establish the importance of episode duration and number of exposure days to initiate beneficial responses. Nonetheless, sustained enhancement of upper airway muscle activity could be important in humans because it could lead to an increase in airway patency and a reduction in the number of breathing events experienced by individuals with obstructive sleep apnea (104, 106). In support of this contention, reductions in upper airway resistance have been reported in patients with obstructive sleep apnea following exposure to intermittent hypoxia (1, 136). Thus intermittent hypoxia might serve as a primary therapeutic treatment to enhance upper airway muscle activity or an adjunctive therapy coupled with other treatment modalities (see subsequent paragraph for additional information) (106). However, for this beneficial effect to be promoted, the potential side effect of chemoreflex enhancement must be eradicated. Therefore the key is to develop a strategy that will minimize or eliminate the potential for exacerbating apnea via enhancement of chemoreflex sensitivity.

Multiple approaches may be employed to promote the beneficial effect on upper airway function. Some of these approaches require further experimental investigation, which is likely worth the effort given the potential benefits of intermittent hypoxia (106). The initial consideration is the timing of the protocol. In a previous study from my laboratory we administered intermittent hypoxia immediately prior to sleep onset because we were interested in the immediate effect of this stimulus on breathing events (165). However, it is possible that administration of intermittent hypoxia many hours prior to sleep onset or at specific times throughout the day/night cycle might promote long-term facilitation in conjunction with chemoreflex properties that would have little to no effect on apnea severity. There is some evidence to support this contention because we showed that the magnitude of long-term facilitation is greater in the evening compared with the morning (51). Studies in animals that have reported a circadian variation in serotonin (2, 108), brain-derived neurotrophic factor, and phosphorylated extracellular regulated kinases (140), which are modulators of long-term facilitation, indicate that this hypothesis is viable (25). Besides timing of the protocol, exposure duration might also promote the benefits of intermittent hypoxia while rendering the detrimental effects impotent. We have shown that repeated daily exposure to intermittent hypoxia results in a reduction in apnea severity in some participants from the initial to the final days of exposure (165). Finally, on the basis of studies completed in a number of laboratories, it is important to ensure that carbon dioxide levels are maintained above baseline values to prevent hypocapnia and the cessation of rhythm generation to both hypoglossal and phrenic motoneurons (60, 63, 151).

Although intermittent hypoxia in conjunction with the maintenance of carbon dioxide above baseline levels may serve to promote beneficial forms of respiratory upper airway motor plasticity and ultimately mitigate breathing events, this protocol might also serve as an adjunct therapy in combination with other treatments (106). For example, enhancement of upper airway respiratory motor function in response to intermittent hypoxia might reduce the continuous positive airway pressure required to treat apnea (106). This would be beneficial because a decrease in pressure might result in increased device com-
The benefits of intermittent hypoxia in treating sleep apnea are primarily theoretical at the present time; however, published experimental findings strongly support the role of intermittent hypoxia in promoting recovery of respiratory (151) and limb motor function in humans with spinal cord injury (64, 153) (Fig. 1). Numerous studies completed in animal models have shown that intermittent hypoxia promotes the recovery of respiratory motor function in C2 spinal cord hemisected rats (47, 54, 158). A crossed phrenic latent pathway in conjunction with the neuromodulator serotonin has a significant role in the recovery of phrenic motoneuron activity (46, 54), although neuromodulators other than serotonin may also have an important role (107). These findings were recently translated to humans. Tester and colleagues showed that exposure to intermittent hypoxia in participants with spinal cord injury enhanced minute ventilation after exposure to the stimulus (151). Results from this study also revealed that improvement in measures of pulmonary function were coupled to the manifestation of long-term facilitation in some participants (151). A case study also demonstrated that improvement in airflow in response to applied resistive loads occurred in a 55-yr-old woman with a chronic spinal cord injury following exposure to intermittent hypoxia (73). Additional outcome measures of respiratory function (e.g., Ppo2 and critical closing pressure) following exposure to intermittent hypoxia in future studies will enhance our understanding of the therapeutic value that intermittent hypoxia has in promoting recovery of respiratory motor function in humans with incomplete spinal cord injury. Intermittent hypoxia also promotes recovery of limb motor function in both rats (94) and humans (64, 153) (Fig. 1). Initial studies in humans with spinal cord injury revealed that electromyography of the gastrocnemius muscle coupled with measures of ankle torque significantly increased following exposure to brief episodes of intermittent hypoxia in humans with injured spinal cords (153). In a subsequent study, exposure to 15- to 90-s episodes of hypoxia each day over 5 consecutive days significantly improved walking speed and duration in 10-m and 6-min walking tests in humans with an incomplete spinal cord injury (64). Interestingly, the effect of daily exposure to intermittent hypoxia on walking speed was enhanced when combined with 30 min of walking each day, which led the authors to conclude that the combined therapies promote greater functional benefits in individuals with incomplete spinal cord injury (64). The improved walking ability observed in humans following exposure to intermittent hypoxia may be due to increased expression of brain-derived neurotrophic factor and phosphorylated tyrosine receptor kinase B via a serotonin-dependent mechanism (23). This mechanism may increase synaptic strength, motor excitability, or both, in respiratory and nonrespiratory motoneurons, in a manner similar to that observed during locomotor recovery after spinal cord injury in rats (94).

### INTERRMITTENT HYPOXIA - COGNITIVE FUNCTION

#### Detrimental Outcomes

Many studies completed in rats have reported that exposure to intermittent hypoxia leads to structural, histochemical, and neurotransmitter changes in many regions of the central nervous system [see (169) for review]. These regions include the hippocampus (CA1 region), frontoparietal cortex, septum, basal forebrain, medulla, pons, and cerebellum (169). The structural changes include but are not limited to diminished excitability in CA1 hippocampal neurons (126, 169), reductions in N-methyl-D-aspartate receptor binding sites (126, 169), and alterations in transcription factors that have a significant role in neuronal survival and memory consolidation in regions of the hippocampus (53, 169). Histochemical alterations reported include increased levels of inducible nitric oxide synthase and cyclooxygenase-2, which initiate pathways that lead to the production of reactive oxygen species (169). In addition, the expression and activity of inflammatory markers increase, and detrimental alterations to cholinergic, dopaminergic, and catecholaminergic systems occur following long-term exposure to severe intensities of intermittent hypoxia (169). These disruptions to specific areas within the central nervous system have also reportedly led to considerable cognitive dysfunction including impairments in hippocampal learning tasks (57, 169), deficits in working memory (132, 133, 169), and hypersomnia (156, 169). The protocols in these studies have often employed severe levels of hypoxia (e.g., 50–72% oxygen saturation) and the duration of exposure has lasted for many hours each day (i.e., 6–24 h), usually for 14 days or longer (109, 124, 134, 135, 156, 157). Thus the risk of exposure to severe intensities of hypoxia over long periods could be accompanied by detrimental cognitive outcomes.

The results from many human studies have also indicated that profound structural damage occurs in the central nervous system of humans with sleep apnea [see review by Harper and colleagues (62)] (Fig. 1). Damaged sites include the primary sensory motor region, ventromedial prefrontal cortex, limbic cortex, hippocampi, and mammillary bodies (62). Many of these sites contribute to the regulation of breathing and control of the autonomic nervous system (62). There is speculation that damage to these areas could contribute to breathing dysfunction, dyspnea, elevated sympathetic nervous system activity, and poor regulation of blood pressure, which have been widely reported in individuals with sleep apnea (62). Likewise, damage described in the anterior cingulate of the limbic system and hippocampus might contribute to the high incidence of depression and anxiety reported in individuals with sleep apnea (29, 62, 97). Finally, injury to the prefrontal cortex, hippocampus, and mammillary bodies could all contribute to impairment in memory and executive function that has been widely reported in individuals with sleep apnea (6, 33, 62, 120). The detection of elevated levels of oxidative stress in humans with sleep apnea (21, 89, 90, 147) coupled with the work completed in animals has led a number of investigators to speculate that damage to the central nervous system is due to oxidative stress, inflammation, and excitotoxic processes initiated by intermittent hypoxia (62, 131, 169).

The role that intermittent hypoxia has in initiating this damage in individuals with obstructive sleep apnea is, how-
ever, debatable (56, 131) (Fig. 1) in part because some animal studies have indicated that other hallmarks of sleep apnea (i.e., sleep fragmentation) lead to damage in similar regions of the central nervous system [see (143) for review]. In addition, studies in healthy humans indicate that sleep deprivation induces functional impairments similar to those observed in individuals with obstructive sleep apnea [see (72, 82) for review]. Finally, results from clinical studies have not been consistent, with some studies failing to find a relationship between measures of oxygen saturation and neurocognitive function (59), whereas others reported that patients with significant oxygen desaturations were more cognitively impaired compared with those with less significant desaturations (127). The most extensive study designed to examine the effect of continuous positive airway treatment on neurocognitive function reported that 6 mo of treatment had no effect on attention, psychomotor function, learning, and memory (87). Alternatively, executive and frontal lobe function was improved (87). However, the improvement was subtle, transient (i.e., it was evident after 2 but not 6 mo of treatment), and evident only in a select groups of patients with severe obstructive sleep apnea (87). This latter finding may be the result of heterogeneity in the population in regards to the severity of the disorder (i.e., intermittent hypoxia) and stimulus response. One possible interpretation of the variable human results is that the mechanistic trigger that initiates central nervous system damage may be multifactorial, and the role of intermittent hypoxia in initiating structural alterations is more likely in individuals exposed to severe levels of hypoxia for long durations of time. However, even the response to severe intermittent hypoxia may not be uniform (17, 164) (Fig. 1).

Evidence of Low-Risk Outcomes

Given that intermittent hypoxia may be an effective research and therapeutic tool, consideration should be given to the possible central nervous system structural, cognitive, and behavioral risk factors associated with the use of intermittent hypoxia. Studies in humans with sleep apnea indicate that research protocols or therapeutic treatments that employ short, moderate-intensity protocols of intermittent hypoxia are likely to be associated with minimal risk in regards to cognitive and behavioral deficits (Fig. 1). Few studies have explored the lack of side effects or positive effects of intermittent hypoxia, possibly because of the viewpoint that exposure to intermittent hypoxia will lead to cognitive dysfunction. Nevertheless, results from completed studies indicate that exposure to a brief protocol of intermittent hypoxia in humans with spinal cord injury for 5 consecutive days was not accompanied by changes in cognitive function as measured by the Mini-Mental state examination (64). Similarly, 4 wk of intermittent hypoxia for 9 h each night did not have a detrimental effect on subjective or objective alertness, vigilance, or working memory in young adult men and women (164). The striking aspect of this particular study was that the duration of exposure was much longer than typically employed in studies investigating the potential therapeutic value of intermittent hypoxia. Ando and colleagues also reported that exposure to a short period of sustained hypoxia (i.e., 10 min) during exercise had no effect on measures of cognitive function despite their initial hypothesis that it would diminish performance during completion of the cognitive tasks (7). To our knowledge, the results from only one study, published in the form of an editorial, reported that intermittent hypoxia leads to deficits in spatial working memory in young healthy adults (17). These deficits were noted following 6 h of exposure to intermittent hypoxia (17). Consequently, the duration of exposure may have played a contributory role in the observed deficits, although Weiss and colleagues reported that exposure to long periods of intermittent hypoxia did not affect cognitive performance (164).

Beneficial Outcomes

Besides having few to no detrimental effects on cognitive function, intermittent hypoxia may also have a role in protecting against cognitive dysfunction (Fig. 1). Although the scope of this review prevents a detailed discussion of the potential mechanisms that promote neuroprotection, they include alleviation of oxidative stress, brain angiogenesis, brain neurogenesis, and promotion of endothelial nitrous oxide formation in response to intermittent hypoxia (98). Studies have shown that brief, intermittent bouts of hypoxia to rats that consumed alcohol prevented overt behavioral signs during subsequent ethanol withdrawal and decreased brain markers of oxidative stress, and preserved the integrity of the mitochondrial membrane during ethanol withdrawal (75, 76). Similarly, exposure to intermittent hypoxia in rats following an ischemic event lead to increases in brain-derived neurotrophic factor, hippocampal neurogenesis, functional synaptogenesis, and alleviated deficits in spatial learning and long-term memory impairment (154, 155). Zhu and colleagues also reported that intermittent hypoxia promotes hippocampal neurogenesis and produces antidepressant-like side effects in adult rats (170). Likewise, given the potential benefits of intermittent hypoxia, this therapy is now being used in experimental animal models of Parkinson (14) and Alzheimer (98) disease with some early success in mitigating the effects of these disorders. Few studies in the literature exist that have examined the benefits of intermittent hypoxia on cognitive function in humans. However, Schega and colleagues reported that intermittent hypoxia enhanced the positive effects that exercise has on cognitive function in elderly humans (138). Furthermore, Rosenzweig and colleagues recently proposed that bilateral enlargement of hippocampi in individuals with obstructive sleep apnea may be the result of compensatory neurogenesis initiated by ischemia/hypoxia preconditioning (130).

SUMMARY

The intention of the present review was to promote the viewpoint that exposure to intermittent hypoxia leads to a variety of physiological benefits with minimal risk. This is contrary to the more popular viewpoint that intermittent hypoxia is generally a high-risk stimulus. Collectively, the published literature indicates that protocols that consist of a small number of episodes that are short in duration and a mild level of hypoxia can lead to significant beneficial outcomes if administered acutely or repeatedly over days or weeks. In some cases, more severe intermittent hypoxia protocols have shown to be low risk or to initiate beneficial physiological outcomes, although the detrimental effects of more severe intermittent hypoxia protocols should remain in the forefront of risk assessment. On the basis of findings in the literature it is impor-
tant to recognize that risk assessment of intermittent hypoxia protocols is dependent on multiple factors and should be completed with a comprehensive understanding of the literature. Further studies are required to discover additional beneficial effects of intermittent hypoxia along with the appropriate dose that promotes these effects while minimizing potential risks.

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AUTHOR CONTRIBUTIONS


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