Physiological and Genomic Consequences of Intermittent Hypoxia
Invited Review: Physiological and pathophysiological responses to intermittent hypoxia

JUDITH A. NEUBAUER
Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, New Jersey 08903-0019

Neubauer, Judith A. Invited Review: Physiological and pathophysiological responses to intermittent hypoxia. J Appl Physiol 90: 1593–1599, 2001.—This mini-review summarizes the physiological adaptations to and pathophysiological consequences of intermittent hypoxia with special emphasis given to the pathophysiology associated with obstructive sleep apnea. Intermittent hypoxia is an effective stimulus for evoking the respiratory, cardiovascular, and metabolic adaptations normally associated with continuous chronic hypoxia. These adaptations are thought by some to be beneficial in that they may provide protection against disease as well as improve exercise performance in athletes. The long-term consequences of chronic intermittent hypoxia may have detrimental effects, including hypertension, cerebral and coronary vascular problems, developmental and neurocognitive deficits, and neurodegeneration due to the cumulative effects of persistent bouts of hypoxia. Emphasis is placed on reviewing the available data on intermittent hypoxia, making extensions from applicable information from acute and chronic hypoxia studies, and pointing out major gaps in information linking the genomic and cellular responses to intermittent hypoxia with physiological or pathophysiological responses.

INTEREST IN THE EFFECTS OF hypoxia is both clinically relevant to discerning the pathophysiological mechanisms of cardiorespiratory diseases and physiologically relevant to understanding the adaptive changes that occur in response to high altitude. As humans have ventured into high altitude as mountain climbers and aviators, it became apparent that we adapt to counter the chronic effects of hypoxia in ways highly beneficial for maximizing the efficient use of oxygen for metabolic demand. The continuum of the response to hypoxia with time is perhaps best documented for sojourners at high altitude. On ascent to altitude, acclimatization to hypoxia is reflected by progressive increases in ventilation, adaptations in the cardiovascular system that enhance oxygen delivery to tissues, and alterations at the tissue level that allow for better extraction of oxygen and more efficient utilization of oxygen for metabolic processes (8, 85). More recent work has focused on determining how these changes are orchestrated by changes in expression of critical gene products (17, 40, 45, 46, 66, 81). The result is that an impressive amount of scientific information has been gathered with regard to the responses to hypoxia, from the integrative systems level to the molecular and genomic level of every organ system.
Although much is known about the acute and chronic effects of sustained hypoxia, less is known about the effects of intermittent hypoxia. Repeated exposures to hypoxia have been examined for both their beneficial and adverse effects. For example, the functional benefits of repetitive hypoxia have been explored for both its therapeutic value in patients and performance value in athletes. However, the clinical pathology of the intermittent hypoxemia associated with sleep apnea syndrome and the apnea of prematurity suggests that there may be long-term adverse consequences of chronic cyclical hypoxia. The pathophysiology of apnea syndromes has spurred a recent surge of interest in the physiological and genomic effects of these persistent, intermittent episodes of hypoxemia that produce a variety of comorbid disorders.

DEFINITION OF INTERMITTENT HYPOXIA

Intermittent hypoxia is broadly defined as repeated episodes of hypoxia interspersed with episodes of normoxia. The actual protocols used experimentally vary greatly in cycle length, the number of hypoxic episodes per day, and the number of exposure days. Thus protocols vary from those that examine the effect of as few as 3–12 relatively short (2–10 min) bouts of hypoxia interspersed with 2- to 20-min episodes of normoxia on a single day (6, 11, 26, 27, 37, 52, 64, 83) to those that examine longer daily exposures (1–12 h) over periods ranging from 2 to 90 days (12, 22, 34, 38, 57–60, 72, 76) and those that examine short sinusoidal cycles of hypoxia/normoxia (30–90 s), 7–8 h daily for 30–70 days (9, 23, 24, 29, 43, 51). Regardless of the protocol, the compelling outcome is that these repeated episodes of hypoxia elicit persistent changes in a variety of physiological responses. Whereas the exact nature of these changes may be dynamically linked to the protocol type, the responses suggest that there is a cumulative effect of intermittent hypoxia that begins with the first exposure to hypoxia. Although there are currently no available data, it is likely that the on and off response times of the underlying cellular and molecular processes determine the reversibility of the adaptive response. Ultimately, the chronicity of intermittent hypoxia may determine whether the response crosses the threshold from having protective value to pathology.

THE BENEFICIAL EFFECTS OF INTERMITTENT HYPOXIA

Intermittent hypoxic training, in addition to providing protection in surviving lethal hypoxia (49), has been proposed to provide protection in certain diseases as well as to improve exercise performance in athletes. The clinical use of intermittent hypoxic training is most recognized by Russian physicians as a therapeutic modality useful in priming the patient for the stress of a host of disease processes. The rationale is based on the cross-protective value of adaptations to one stress providing resistance to another stress (44, 54, 84). Adaptation to stress results in enhanced expression of stress proteins and antioxidant systems that can then provide protection against the generalized stress of disease (53). There is literature to support this concept of cross-protection. For example, intermittent hypoxic training has been shown to have a significant antiarrhythmic effect in acute myocardial ischemia in conscious animals (55, 56) and to prevent experimental atherosclerosis in rabbits (38). The protection of the myocardium has been shown to correlate with the ability of intermittent hypoxia to increase myocardial vascularity, coronary blood flow, and cardiomyoglobin as well as to increase expression of antioxidant enzymes and stress proteins (89). Of note is that intermittent hypoxic episodes produce adaptations similar to those of continuous chronic hypoxia and that these adaptations, by their nature, provide protection from the oxidative stress of a variety of disease processes.

Intermittent hypoxic training is more universally recognized by the sports medicine community as a useful strategy to enhance exercise performance in athletes (25). In this case, “living high” and “training low” promote the hematological and ventilatory adaptations of hypoxic acclimatization to improve performance capacity without eliciting the adverse effects of chronic hypoxia. For example, intermittent hypoxia is an effective stimulus for erythropoietin production in both humans (39, 41, 75) and rats (58). Although protocols vary somewhat, most intermittent hypoxic training programs expose healthy subjects to episodes of either hypobaric or hypoxic hypoxia daily (4–6 h) over a 2-wk period. The results of these training programs are fairly impressive. Intermittent hypoxic training increases exercise time, total red blood cells, and hemoglobin, reduces the heart rate response to exercise, and shifts the lactate to exercise load to the right with an increase in ventilation at threshold (12, 71, 72, 74). Intermittent hypoxic training also causes an increase in the hypoxic ventilatory response (36, 78, 79).

There are, however, some important differences in the responses to continuous chronic hypoxia and exposure to intermittent hypoxia. One is their differential effect on the classic biphasic respiratory response to hypoxia, that is, the well-documented, time-dependent response to hypoxia in which there is an initial increase in ventilation that is followed after 3–5 min by a hypoxic ventilatory decline (20). In contrast to continuous hypoxia, which significantly reduces the initial increase in ventilation and increases the magnitude of the hypoxic ventilatory decline, intermittent hypoxia abolishes the hypoxic ventilatory decline in both adult humans (64) and neonatal rats (27). This may well be linked to the specific ability of episodic hypoxia to alter respiratory neuronal activity. Episodic hypoxia produces a long-lasting increase in normoxic ventilation (11) due to an induction of a serotonergic-dependent long-term facilitation of respiratory activity (37, 83), whereas continuous hypoxia does not (19). Finally, variations in the responses to intermittent hypoxia may also be determined by differences in genetics. Kraicz et al. (43) found that chronic intermittent hypoxia increased the blood pressure response to hypoxia, heart size, and atrial natriuretic peptide mRNA in
spontaneously hypertensive rats but not their genetic controls, the Wistar-Kyoto rats.

PATHOPHYSIOLOGICAL EFFECTS OF INTERMITTENT HYPOXIA

With so much interest in the potential usefulness of intermittent hypoxia to improve the body's ability to withstand the stress of disease, improve exercise performance, and enhance the respiratory response to acute hypoxia, what could be bad? Certainly, there are adaptations to chronic hypoxia that are not necessarily beneficial. Chronic intermittent hypoxia significantly increases right ventricular heart mass, likely associated with pulmonary vascular remodeling and pulmonary hypertension (6, 34, 51, 59, 60). There are also detrimental effects on normal development, especially in the fetus because intermittent hypoxia significantly decreases fetal growth (22, 76). However, it is the association of hypertension, developmental defects, neuropathological and neurocognitive deficits, enhanced susceptibility to oxidative injury, and possibly increased myocardial and cerebral infarction in patients with obstructive sleep apnea (OSA) syndromes (73) that has fostered an intense interest in examining the link between intermittent hypoxia and these adverse events. OSA is characterized by episodic obstructions of airflow during sleep, often more than 60 times per hour, with significant desaturations of hemoglobin to levels as low as 50%. These events are not only associated with hypoxemia but significant hypercapnia and frequent arousals leading to significant sleep fragmentation as well. Thus the specific role of intermittent hypoxia in producing the major clinical consequences of OSA has been difficult to sort out from clinical studies. In the general US population, 9% of women, 24% of men (86), and 2% of children (47) have been diagnosed with OSA, suggesting that 18 million people may suffer from the consequences of nightly episodes of apnea. Thus the need to understand the impact of chronic cyclical hypoxia alone, as well as in combination with cyclical hypercapnia and arousals, on physiological responses at the cellular, molecular, and genomic level must be a high priority.

Of the many pathophysiological consequences of OSA, the association of hypertension with OSA is quite strong, even after obesity is removed as a confounding risk factor (63, 68, 87). Experimental studies in dogs (10) and rats (24) support the hypothesis that intermittent hypoxia and not sleep fragmentation causes persistent hypertension. Using experimental protocols that simulate the clinical syndrome of OSA, these investigators showed that cyclical hypoxia alone causes an increase in daytime blood pressure. This sustained increase in blood pressure appears to be due to an enhanced sympathetic activity (9) and can be prevented by sympathetic denervation using 6-OH dopamine (23). Chronic intermittent hypoxia also significantly enhances the sympathetic and blood pressure responses to acute hypoxia and hypercapnia (29, 31, 43). Whether this adaptation in sympathetic activity involves a central or peripheral site is currently not known.

One potential site of adaptation is within the sympathoexcitatory region of the rostral ventrolateral medulla, since neurons in this region are sensitive to the direct effects of hypoxia (50, 82).

The role of intermittent hypoxia as causative for the other major clinical consequences of OSA is largely unexplored. Studies similar to those just described demonstrating the ability of intermittent hypoxia to cause sustained daytime hypertension have not been done to examine their link with cyclical hypoxia. OSA does produce short- and potentially long-term neurocognitive deficits (69) but whether this is a function of the hypoxia, hypercapnia, or sleep fragmentation associated with repetitive apneic events is not clear. Intermittent hypoxia in the antenatal period has been shown to lead to long-term changes in the behavior and neurochemistry of rats (32, 57). Alterations in cerebral synaptosomal ATPase activities can also be induced with intermittent hypoxia (7). These changes would be expected to affect neurotransmission by their effects on production of adenosine and the turnover of neurotransmitters. Intermittent hypoxia has also been shown to impair cerebral lipid metabolism (1) and produce regional changes in the activities of key metabolic enzymes in the brain (48) and in the concentrations of brain stem methionine-enkephalin (26) and serotonin (52). However, the consequences of intermittent hypoxia on brain oxygenation and metabolism and whether repetitive oxidative stress can lead to neuronal injury and perhaps exacerbation of neurodegenerative disease processes are not defined. The cascade of events that could lead to such injury is not hard to imagine because even brief episodes of hypoxia produce changes in metabolic pathways, angiogenesis, and even inflammatory responses that could underlie short- and long-term changes in neuronal functions. Some of these changes are adaptive responses to persistent hypoxia aimed at preserving brain oxygen and improving metabolic efficiency. For example, hypoxia excites reticulospinal neurons in the rostral ventrolateral medulla responsible for initiating autonomic responses associated with oxygen-conserving reflexes (70). However, others, such as those mediating vascular changes, may have limited adaptive value.

Chronic hypoxia induces proliferation of the vasculature due to angiogenesis but can also change the integrity of vessels, leading to changes in vascular permeability. A host of growth factors, including vascular endothelial growth factor (VEGF), interacting with integrins orchestrates the formation and maintenance of blood vessels. Hypoxia influences the dynamics of the processes inducing angiogenesis primarily through its ability to upregulate VEGF (67, 80). The effects of intermittent hypoxia on angiogenesis and vascular integrity have not been examined. However, chronic hypoxia is well known for its ability to increase capillary density as well as to cause acute mountain sickness by destabilizing vascular integrity, resulting in leakage of proteins and water through the blood-brain barrier, which leads to impaired brain function (30). In addition, if intermittent hypoxia results in abnormal angiogenesis, it may contribute to the in-
increased incidence of cerebral infarction associated with OSA.

The ability of hypoxia to promote persistent adaptations is due in part to its ability to induce changes in gene transcription. The regulation of the expression of a wide variety of genes involved in hypoxic adaptations is largely due to activation of a hypoxia-sensitive transcription factor, hypoxia-inducible factor 1 (HIF-1) (77). HIF-1 is a heterodimer of HIF-1α and HIF-1β. Oxygen levels directly regulate the expression of the HIF-1α component in a dose-dependent manner, with a gradual increase from 20 to 5% O₂ and a pronounced increase below 5% O₂ (35). Tissue Po₂ is normally 20–40 Torr, suggesting that HIF-1 is exquisitely sensitive to changes in tissue oxygenation. The dynamics of HIF-1α expression also appears to be quite rapid both in its onset of expression and its decay characteristics. For example, evidence of decay of HIF-1α after reoxygenation of lung tissue occurs in <1 min (88). Such rapid dynamics could provide the ability for short bouts of intermittent hypoxia to produce adaptations at the level of gene transcription that promote angiogenesis, erythropoiesis, and glycolysis. Thus, although no data are available regarding whether tissues respond differently to continuous or intermittent hypoxia, it seems reasonable to expect that HIF-1 expression is a critical determinant in initiating and reversing the adaptive and/or maladaptive responses to intermittent hypoxia.

There is abundant literature documenting the effects of hypoxia on neuronal activity at both pre- and postsynaptic sites (8, 62) and the conditions that need to be met to induce brain injury (3). However, whether chronic or intermittent hypoxia can induce neuronal injury via neurotoxic mechanisms and thereby explain the deficits in neurofunction associated with chronic repetitive hypoxia is speculative at best. Excitotoxicity is generally thought to be initiated by severe metabolic stresses resulting in significant calcium influx through activation of glutamergic receptors (2). In addition, brain injury resulting from generation of reactive free radicals during hypoxia can occur as well (4, 15). Although there may be adaptations that promote increases in the antioxidant defenses, the different nature of these reactions do not necessarily assure protection because these reactions may produce species that are more toxic not less toxic. For example, the more toxic nature of superoxide bound to iron sulfur complexes in the mitochondria and the reaction of nitric oxide with free radicals to produce the highly reactive peroxynitrite (5) could have significant damaging effects on the cell. Peroxynitrite directly oxidizes many proteins, resulting in nitration of tyrosine (42), which, depending on the protein, may result in protein activation or inactivation. In fact, peroxynitrite can ultimately induce apoptosis (65), although susceptibility is highly dependent on the presence or absence of a variety of trophic factors (21). Little information is available as to which trophic factors are protective and which accelerate cell death, but clearly such information would be of value in the clinical management of pathophysiologic disorders associated with intermittent hypoxia.

Cell injury may also occur due to the effect of hypoxia on mitochondrial function. Mitochondria are an important source of reactive oxygen species and generally are fairly efficient at scavenging free radicals. However, recent evidence suggests that the mitochondrial genome is particularly vulnerable to oxidative stress because it has no mechanisms for repairing damaged DNA (13). The mitochondrial genome codes for the key proteins involved in synthesizing ATP; thus mutations of the mitochondrial DNA can result in abnormalities of the electron transport chain. The ability of mitochon-
tion. For example, it ups the ante with regard to developing the methodology for early diagnosis and treatment of the intermittent hypoxia of apnea syndromes and their consequences.

REFERENCES

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