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Mini Review

Physiological Effects of Intermittent Hypoxia

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ABSTRACT

Powell, Frank L., and Nathalie Garcia. Physiological effects of intermittent hypoxia. ***High Altitude Med Biol*** **1:125–136, 2000.—**Intermittent hypoxia (IH), or periodic exposure to hypoxia interrupted by return to normoxia or less hypoxic conditions, occurs in many circumstances. In high altitude mountaineering, IH is used to optimize acclimatization although laboratory studies have not generally revealed physiologically significant benefits. IH enhances athletic performance at sea level if blood oxygen capacity increases and the usual level of training is not decreased significantly. IH for high altitude workers who commute from low altitude homes is of considerable practical interest and the ideal commuting schedule for physical and mental performance is being studied. The effect of oxygen enrichment at altitude (i.e., intermittent normoxia on a background of chronic hypoxia) on human performance is under study also. Physiological mechanisms of IH, and specifically the differences between effects of IH and acute or chronic continuous hypoxia remains to be determined. Biomedical researchers are defining the molecular and cellular mechanisms for effects of hypoxia on the body in health and disease. A comparative approach may provide additional insight about the biological significance of these effects.

Key Words**:** acclimatization; chronic hypoxia; erythropoiesis; exercise training; hypoxic ventilatory response; long-term facilitation; Mount Everest; sleep apnea

THIS MINI REVIEW considers intermittent hypoxia (IH), which we define as exposure to hypoxia lasting minutes to days that is repeated over several or more days. Intermittent bouts of hypoxia are separated by return to normoxia or levels of hypoxia that are less severe (higher PO_2). Some patterns of IH we review could be considered as "intermittent normoxia" when a baseline condition of hypoxia is broken by intermittent exposure to normoxia (or less severe hypoxia). However, we argue that the most important question for all patterns of IH relates to how the response to it differs from the response to either (1) a single acute exposure to hypoxia or (2) exposure to continuous chronic hypoxia (CH). It will be important to determine the effects of different "doses" of hypoxia too, in terms of the depth

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of hypoxia and pattern and total duration of exposure. We focus primarily on environmental hypoxia defined as a decrease in inspired PO_2, as occurs upon ascent to high altitude. To maintain a reasonable scope for this mini review we only consider other interesting and important forms of periodic oxygen deprivation, such as arterial hypoxemia that may occur with sleep apnea, to illustrate potential mechanisms and alternative applications of IH. Also, we selected representative references to illustrate major points and do not intend this to be a comprehensive review of all of the important studies performed to date on IH.

Recent interest in this topic has led to new studies showing significant differences between IH and CH. There is a significant literature on the mechanisms of response to CH and how they differ, or result from, the effects of acute hypoxia. Most of the studies to date on IH can be considered "descriptive" in contrast to studies testing hypotheses about mechanisms of action of CH, for example. Also, most of the studies to date focus on oxygen transport, but illustrations are provided for the effects of IH on other physiological systems too. We focus on mechanisms of acclimatization to hypoxia, including the time-dependent increases in ventilation, increases in the hypoxic ventilatory response (HVR) and erythropoiesis, which are well characterized for CH (Weil, 1986; Powell et al., 1998; Milledge, 2000).

HIGH ALTITUDE MOUNTAINEERING

Acclimatization schedules

IH has been an integral part of high altitude mountaineering for years. Climbers ascend from low altitude base camps to higher altitudes where they establish camps to stage for their summit attempts. Typically they return to base camp for more supplies and sleep. Over the days and weeks that are necessary to climb very high altitude peaks (>8000 m), this pattern of up and down results in IH exposures that are typically increasing in the degree of hypoxia (Fig. 1). This pattern originated out of logistical necessity, but it is now well established that climbers should sleep at as low of an altitude as possible, while still obtaining adequate acclimatization and meeting the climbing schedule for a successful summit bid. Avoiding the sleep deprivation, dehydration, malnutrition, and general deterioration that accompany life at extreme altitude is essential for successful high altitude mountaineering.

More recently, IH has been viewed as a way to potentially speed up or improve acclimatization. The tragic events on Mount Everest in 1996 focused attention on IH as a means to gain rapid acclimatization. Traditionally, acclimatizing in the Himalayas is achieved by slowly ascending to altitude during a long trek. In contrast, the recent guided trips taking paying clients to the highest summit on earth have a strong profit motive to minimize the total time for an expedition. Fortunately, this strategy agrees with the conventional approach based on experience and medical science as described above. For example, Anatoli Boukreev, who guided on the 1996 Mountain Madness expedition to Mount Everest, stated that "Our job is to get clients the necessary acclimatization with a minimal number of nights at high altitude camps" (Boukreev and DeWalt, 1997).

Scientific studies of IH and mountaineering

Several groups have studied the applied physiology of IH as a means of preacclimatization to improve climbing performance at high altitude. Although it is not well studied, the rate of deacclimatization is not always as rapid as the rate of acclimatization to altitude (Milledge, 2000). This suggests that IH may result in a net acclimatization. One of the earliest studies was by Nagasaka and Satake (1969) who hypothesized that IH could produce acclimatization more efficiently than CH. To mimic the usual climbing pattern of mountaineers during an expedition, they exposed 12 subjects to simulated altitude in a hypobaric chamber. After 3 consecutive days simulating 6000 m (354 mmHg) for 5 h and 8000 m (270 mmHg) for the next 1 h, they observed an increase in $\dot{V}_I$ and PaO_2 in hypoxia, indicating the initiation of ventilatory acclimatization.

Subsequent studies exposed resting humans to IH simulating altitudes above 5000 m as a preacclimatization training method for moun-

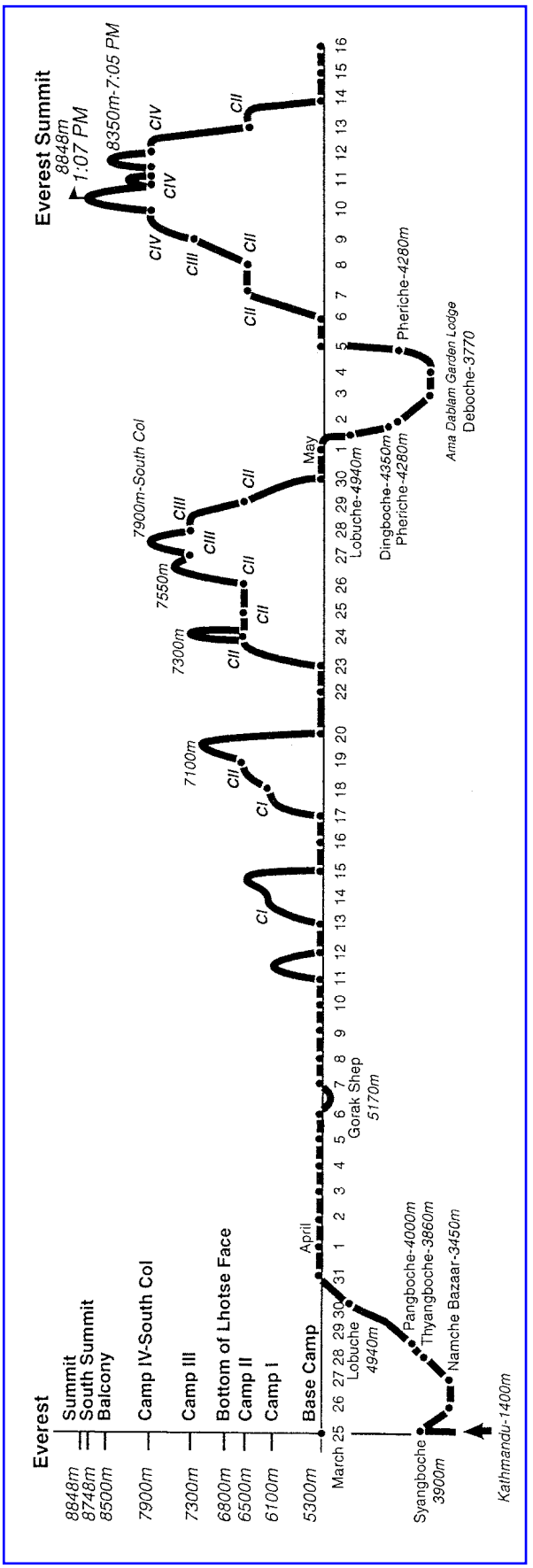

FIG. 1. Altitude profile for Anatoli Boukreev on 1996 expedition to Mount Everest. Different patterns of intermittent hypoxia are shown as ascents followed by descents in an effort to maximize acclimatization to hypoxia at altitude and reduce the detrimental effects of hypoxia on performance. (Modified from Boukreev and DeWalt, 1997.)

taineering expeditions (Richalet et al., 1992, 1999a; Savourney et al., 1996). Others used less severe hypoxic stimuli (simulated altitudes of 2500 to 5000 m), but added exercise to the IH and also measured the effects of such IH on the hypoxic ventilatory response (HVR) (Benoit et al., 1992; Levine et al., 1992; Katayama et al., 1999; Rodriguez et al., 1999). In general, these studies showed increases in the HVR and ventilation and arterial saturation (SaO_2) during hypoxia. Hence, the studies show ventilatory acclimatization to IH is qualitatively similar to CH, although they did not specifically compare the two patterns of hypoxia. Also, some of the protocols actually combined stimulus patterns by administering CH before IH (Richalet et al., 1992, 1999a).

Effects of IH on performance measured as $\dot{V}O_2$ max at altitude show little or no change. Proper controlled studies to demonstrate benefits of IH for high altitude mountaineering have not been done. Richalet et al. (1992) exposed five "elite climbers" to CH followed with IH plus exercise before an expedition to Mount Everest, although these climbers were not able to make any final summit bids because of bad weather. It has been impossible to quantify performance on the mountain between such experimental groups and other climbers because the acclimatization history of the other climbers is so different and unknown.

TRAINING FOR ATHLETIC PERFORMANCE AT LOW ALTITUDE

Athletes and coaches have considered the potential benefits of "training" the oxygen transport system at altitude to improve performance at sea level. Public interest in this approach began with preparation for the 1968 Olympics in Mexico City, at 2380 m above sea level, and has continued in recent years with the scandals around the Tour de France involving blood doping and erythropoietin abuse to increase hematocrit. Increased oxygen delivery (e.g., hyperoxia, increased hematocrit) can increase $\dot{V}O_2$ max (Buick et al., 1980; Powers et al., 1989). The problem with using altitude acclimatization to enhance physiological oxygen transport is that $\dot{V}O_2$ max decreases at altitude so athletes actually "detrain" at even moderately high altitude (e.g., 3000 m) because they cannot train as hard as they do at sea-level.

A solution to this dilemma is an IH strategy used by aerobic athletes termed "living high-training low." For example, Levine and coworkers showed that 5000 m running times were improved in athletes who lived at moderately high altitude (2500 m) but trained at 1200 m altitude several hours each day for 4 weeks (Levine and Stray-Gundersen, 1997). This contrasted with athletes who lived and trained at either moderately high or low altitude exclusively. There was individual variation between athletes, but those who responded best to the living high-training low strategy showed the largest erythropoietic response and an increase in $\dot{V}O_2$ max that was proportional to the increase in hematocrit (Chapman et al., 1998).

It is common knowledge that more applied research has been done on this topic by various Olympic teams, but it is not in the public literature because of the competitive nature of sports. The popularity of this concept is evidenced by advertisements in sports magazines for portable hypoxia chambers so one can "live high" (or rather sleep high) in their usual low altitude training environment. These chambers are also advertised in climbing magazines as a strategy for preacclimatization by IH.

WORKING AT HIGH ALTITUDE

The opportunities for work at high altitude are increasing with the extensive development of commercial and scientific activities in high mountain ranges. Notable examples include mining in South America and high altitude observatories for optical and radio telescopes, both involving altitudes of 3500 to 6000 m (reviewed by West, 1998, 1999; Heath and Williams, 1995). With these opportunities come large-scale challenges to public health and worker safety, as well as problems in maintaining worker productivity and morale. Worker productivity relates to the employee's ability to function efficiently, physically and mentally, in a hypoxic environment. Worker morale relates to the hardships of living at high

altitude. Not only are there direct physical effects on the employees, but the harsh environment precludes families from residing near the work place and leads to workers commuting between home at low altitude and the high altitude work site. Solutions to all of these problems involve defining the ideal acclimatization schedule that necessarily involves IH.

Commuting to high altitude

In general, a commuting strategy is the same as the acclimatization strategy for high altitude mountaineering, that is, descending to low altitude when possible for rest and recovery. One goal in this strategy is to eliminate or minimize the loss of any acclimatization to hypoxia while normoxic (or less hypoxic). The benefits for different commuting schedules remain to be determined but are under active study. Influences of shift working in the Chilean Andes on erythropoiesis (Gunga et al., 1996) is discussed later. A larger 3-year-long prospective study was begun in February 1998 to characterize miners in North Chile working at 4300- to 4600-m altitude (Richalet et al., 1999b). An experimental group, working 7 days at altitude and resting 7 days at sea level, will be compared with a control group living permanently at sea level. Physiological and psychological studies are being repeated every 8 months. It would be interesting to compare the results of the experimental IH group with a group exposed to CH at the same altitude also, but this would be logistically difficult given the hardships explained above.

In practical terms, commuting to high altitude is most important for sites above 4000 m, as evidenced by extensive human development at altitudes between 3800 and 4100 m in the Himalayán and Andean regions. Our own observations on workers at 3800 m altitude (Barcroft facilities at the University of California White Mountain Research Station) support this concept also. These workers report that the commuting schedule is not important in terms of their physiological performance or well-being at this moderately high altitude. Employees work at altitude continuously for 7 days followed by 7 days off, during which time they are generally at 1235 m (in Bishop, California). However, they may be anywhere between sea level and higher altitudes on recreational trips. Interestingly, they all report feeling more sluggish at low altitude but proper studies have not been done to rule out effects of temperature, psychological factors (e.g., domestic stress), etc.

Oxygen enrichment at high altitude

Another strategy for dealing with the challenge of living and working at altitude is oxygen enrichment of living and working spaces. Similar to the use of air conditioning, the temperature in a room for optimum comfort or performance, oxygen enrichment can be used to simulate lower altitudes and optimize performance. West (1995) has described the theoretical and engineering aspects of this technology. At moderately high altitudes where modern commercial activity is concentrated (3000 to 6000 m), enriching the oxygen concentration of ambient air by 1% decreases the effective altitude by approximately 300 m. Hence, with modern oxygen concentrator technology, it is economically feasible to lower the effective altitude over 1000 m in defined spaces such as sleeping dormitories or control rooms of high altitude work places. Personal oxygen concentrators, manufactured for patients needing supplemental oxygen at home, cost less than US$1,500, require about 350 W of electrical power and generate sufficient oxygen (3–5 L/min of >90% O_2) to raise ambient O_2 by 3% in a small room with normal levels of ventilation (West, 1995).

Recently, the feasibility and physiological consequences of using this technology have been studied in an oxygen conditioned room in the Barcroft facilities at the University of California White Mountain Research Station (3800 m altitude). Luks et al. (1998) used a double-blind, randomized protocol to study the effects of sleeping with 3% O_2 enrichment (simulating 2900 m) on sleep and subsequent daytime performance at 3800 m. Predictably, O_2 enrichment significantly reduced sleep apnea and improved the reported quality of sleep. However, there were also some significant changes during the day at 3800 m *after* subjects had slept at lower simulated altitudes the night before. Acute mountain sickness decreased signifi-

cantly and SaO_2 increased significantly after O_2 enrichment. The physiological mechanisms for these changes remain to be determined.

In contrast, Burse and Forte (1988) found that IH (8 h of 3370 m simulated altitude/day for 8 days) did not decrease acute mountain sickness upon exposure to 4500 m, relative to controls. The investigators hypothesized that more severe IH might prevent it because anecdotal observations showed that 3 to 4 days of exposure to 4–6 h at 4300 m (on Pikes Peak, CO) enabled most individuals to remain at that altitude for 16–48 h without developing severe symptoms of acute mountain sickness.

A second study using this facility focused on the benefits of O_2 enrichment at higher altitudes for cognitive versus motor function (Gerard et al., 2000). Nitrogen enrichment was used to simulate 5000 m (PIO_2 = 78 T) and O_2-enrichment was used to simulate 3200 m (PIO_2 = 100 T) in the oxygen conditioned room. In a battery of 16 tests, some aspects of motor function and "physiological" attention (e.g., hand–eye coordination) improved significantly, "cognitive" attention (e.g., memory, calculation) did not. One's sense of well-being was improved by O_2 enrichment also. Hence, workers feel better with O_2 enrichment at this altitude, but if they are involved in mental work that does not require physical coordination, and they are highly motivated like the test subjects in this study, there is no demonstrable benefit. These results should be of interest to astronomers who recognize problems in operating high altitude telescope facilities (Cudaback, 1984; Napier and West, 1997).

Two important unanswered questions are: "What are the effects of prior intermittent O_2 enrichment on cognitive versus motor function in ambient conditions at high altitude?" "Are the benefits of O_2 enrichment during the day and during sleep at night similar?" This is relevant for workers that may have to leave an O_2-enriched environment to complete some aspect of their job outside. Concern has been expressed that performance under such acute increases in hypoxic stress may be worst but this has not been tested. Similar to mountaineers descending to lower altitude for rest and athletes "living high-training low," the pattern of IH with O_2 enrichment is technically intermittent *normoxia* on a background of chronic hypoxia. Determining the effects of such differences in the temporal patterns of hypoxia and normoxia is another problem that remains to be investigated.

LABORATORY STUDIES OF IH

Probably the first laboratory investigation of IH was conducted in a hypobaric chamber by Haldane and colleagues (1919). Altitude tolerance was increased by as little as 3 days exposure to 500, 450, and 360 T with nights spent outside the chamber. One can speculate that this protocol was dictated by logistical or domestic concerns instead of scientific concerns, however. West (1998) points out that the last day of the experiment was cut short as Haldane "came out about 4:00 p.m., as it was necessary to catch a train."

Ventilatory acclimatization

Recent laboratory studies of IH are focusing on aspects of physiology other than athletic performance at high altitude. The literature oriented toward mountaineering (discussed above) has not determined (1) the time course of acclimatization in IH; (2) the effects of different levels and duration of hypoxic exposure, that is, the "dose" of IH; (3) the effects of exercise training versus hypoxia and their potential interaction; and finally (4) the efficacy of IH versus CH and differences in mechanisms of acclimatization to the two stimulus patterns. Recently, we tried to address these issues by measuring the time course of ventilatory and hematological change in humans exposed to a protocol of moderate IH at rest. The study was designed to give a lower "dose" of hypoxia than previous IH studies by simulating only 3800 m altitude (PIO_2 = 90 T) for 2 h per day, for 12 consecutive days and exercise training was *not* part of the study (Garcia et al., 2000a). Finally, the results were compared with exposure to CH for 2 days to 8 weeks (Garcia et al., 2000b).

The time course of change in the HVR appeared quantitatively similar with IH and CH, but on a compressed time scale with IH. In IH the isocapnic HVR (with end-tidal PCO_2 held

constant as inspired PO_2 decreased) significantly increased to a maximum value at 5 days and subsequently decreased toward control levels by 12 days at the end of the protocol. In CH we observed a monotonic increase in HVR during the first 2 weeks, similar to other studies (Sato et al., 1994), but this was followed by nonsignificant decrease between 3 and 8 weeks of CH. Another similarity between IH and CH was the maximum increase in the HVR observed, although they occurred at different times. It remains to be determined if similar physiological mechanisms are responsible for changes in the HVR during IH and CH, and even if there is a secondary decrease in HVR during several weeks of CH. Blunting of the HVR with years of exposure to hypoxia is well known (Weil, 1986; Powell et al., 1998), but the HVR has not been studied over a few months.

Despite the fact that this modest level of IH without accompanying exercise can increase the HVR, ventilation and SaO_2 were not significantly increased in hypoxic or normoxic conditions at any time during the IH protocol. This is consistent with the idea that isocapnia enhances changes in the HVR; the increase we measured may not have a physiologically significant effect on $\dot{V}_I$ and SaO_2, given the hypocapnia that accompanies air breathing at altitude. However, we estimated that HVR increased similarly with IH and CH and Sato et al. (1994) showed that the increase in HVR contributed to increased ventilation and SaO_2 at this altitude (Sato et al., 1994). To repeat, more studies are needed comparing IH with CH to determine if fundamentally different mechanisms are involved. However, it is clear that this modest level of IH will not be useful for preacclimatization, assuming the benefits of preacclimatizing result solely from increased ventilation and arterial oxygenation under hypoxic conditions. Such studies are probably more important for determining the basic physiological mechanisms of time-dependent changes in ventilatory control by explaining differences between effects of IH or CH.

Hematological effects of IH

Hematological responses to IH in humans have been studied less than ventilatory acclimatization. Decreased plasma volume in CH contributes to increased hematocrit at altitude (Milledge, 2000), but the effects of IH on blood component volumes have not been studied. Levine and Stray-Gundersen (1997), using their "living high-training low" IH protocol described above, found results similar to CH, that is, plasma volume decreased and red cell volume increased. Other studies of IH in humans have not measured plasma volume, but they have not revealed significant changes in hemoglobin concentration or hematocrit (Richalet et al., 1992, 1999; Savourney et al., 1996; Rodriguez et al., 1999a; Garcia et al., 2000a). Although hematocrit may not increase with IH, reticulocyte count and erythropoietin concentration increase in some cases (Savourney et al., 1996; Leadbetter et al., 1999; Richalet et al., 1999a; Garcia et al., 2000a). Increased erythropoietin may not have been detected in protocols with blood sampling immediately before and after short, daily bouts of IH because it requires 2 h of hypoxia to increase in humans and has a half-life of about 5 h (Eckardt et al., 1989).

Alternatively, IH may have stimulated the early release of premature red cells, including reticulocytes. Gunga et al. (1996) found increased reticulocytes in cooks commuting to work in high altitude mines (>5 years of 10 days at 3600–4000 m followed by 4 days at sea level), but no change in serum transferring receptor concentration. This is strong evidence for increased reticulocyte count without erythropoiesis. However, these high altitude commuters had normal erythropoietin responses to acute hypoxia so this problem needs further study.

IH IN DISEASE

IH is an important, but poorly understood topic in cardiopulmonary disease. Many disease processes occur episodically, especially as they are developing, and many therapies are not successful at completely alleviating arterial hypoxemia or tissue hypoxia in a continuous and sustained manner. Medical scientists are interested in the concept that physiological responses to an acute hypoxic insult may be different—either blunted or enhanced—by previous exposure to hypoxia. This idea has been discussed extensively in the Russian literature

in terms of "cross adaptation," that is, adaptation to one stress improves tolerance to another. IH is proposed as beneficial for a myriad of ailments (e.g., age and Parkinson's Disease; Serebrovskaya et al., 1999). It has also been studied in terms of specific consequences of hypoxic preconditioning on cerebral and coronary ischemia, as may occur with transient ischemic events (strokes) and mild heart attacks (Ruscher et al., 1998; Levy, 1999).

Sleep apnea

Obstructive of central sleep apnea results in IH and a suite of systemic human diseases including hypertension. Rats exposed to IH that changes SaO_2 in a pattern similar to humans with sleep apnea (3–6 sec hypoxia followed by a return to normoxia over 15–18 sec, repeated twice per min, 6–8 h per day) also develop hypertension (Lesske et al., 1997). Experiments on this IH model indicate that hypoxic stimulation of arterial chemoreceptors and the adrenals leads to increased sympathetic activity and this is associated with elevated blood pressure. However, there is little direct evidence for a sympathetic mechanism of hypertension with chronic IH or sleep apnea. Human studies show that treatment of sleep apnea with continuous positive airway pressure breathing (CPAP) decreases sympathetic activity without affecting the baroreflex or decreasing blood pressure (J.E. Dimsdale, J.L. Clausen, and M. Ziegler, personal communication, 1999). The effects of supplemental O_2 at night, which also decreases sleep apnea, IH and arterial chemoreceptor stimulation (Phillips et al., 1990), on hypertension remains to be investigated in patients at sea level. The physiological mechanisms of IH during sleep apnea on blood pressure are considered below.

PHYSIOLOGICAL MECHANISMS OF IH

The physiological effects of IH may differ from those stimulated by acute hypoxia because of hysteresis or memory-like effects in the systems responding. Hysteresis could result from a mismatch between the time constants of a physiological process and the frequency of stimulation by periodic hypoxia. For example, a response to hypoxia may "turn on" more quickly than it "turns off" when normoxia is restored or hypoxia is reduced. The same principle applies to attaining a therapeutic dose of a drug by repeated administrations of smaller doses (and is described by pharmacokinetic models). Memory-like effects involve plasticity, or changes in structures (e.g., synapses) or fundamental processes (e.g., cell-signaling pathways) in a control system. There can be interactions between these two classes of mechanisms too; for example, with hysteresis in mechanisms of neural plasticity induced by hypoxia.

Arterial chemoreceptor reflexes

It follows that the physiological responses to IH will depend upon the dynamic response characteristics of the relevant sensory system. Arterial chemoreceptors in the carotid and aortic bodies are the most important sensory organs for hypoxia and they respond to decreases in PO_2, rather than O_2 content or saturation (Fitzgerald and Lahiri, 1986). Afferent neural output from arterial chemoreceptors responds rapidly to changes in PaO_2 and faithfully track changes in PaO_2 oscillations up to normal breathing rate (Fitzgerald and Lahiri, 1986). Hence, the arterial chemoreceptors can respond to such brief periods of IH as may occur during sleep apnea, as described above. The reflex response of arterial chemoreceptor stimulation includes ventilatory and cardiovascular responses, so IH may contribute to hypertension in sleep apnea, as described above also. Marshall (1994) has thoroughly reviewed the literature and presents strong evidence that arterial chemoreceptor stimulation evokes the cardiovascular component of the alerting stage of the defense response. Different components of these sympathetic nervous system effects on the cardiovascular system have different time constants so it is reasonable to hypothesize that blood pressure responses to IH may differ from acute hypoxia or CH. The effects of CH on the sympathetic nervous system and cardiovascular control have, and are, being studied intensely so we are accumulating a wealth of baseline data (Milledge, 2000). Considering the

potential relevance of IH to cardiovascular disease, this suggests that a major focus of future studies of IH should be the autonomic control of cardiovascular function.

The ventilatory responses to IH and different patterns of afferent input from arterial chemoreceptors have been studied more intensively and they show hysteresis. A good example is long-term facilitation of ventilation (LTF). In anesthetized or awake animals, but not awake humans, ventilation remains above control levels for an hour or more following IH consisting of 3 to 5 alternating bouts of hypoxia and normoxia, each lasting 2 to 5 min (Powell et al., 1998). LTF also occurs as an increase in ventilation following repeated bouts of electrically stimulating carotid body afferent nerves and it has been shown to depend on neuronal mechanism in the respiratory centers of the brain stem. LTF involves serotonin and changes in cell signaling (McCrimmon et al., 1995). LTF is clearly distinct from other time-dependent changes in ventilatory chemoreflexes that occur during CH (Powell et al., 1998). Therefore, IH may have secondary effects on neural control systems by increasing nerve traffic through specific pathways and inducing use-dependent changes in neural properties (e.g., synaptic transmission) independent of hypoxia per se. The ventilatory chemoreflexes may serve as models for understanding other neural control systems operating during IH.

Cellular and molecular effects of hypoxia

Hypoxia is also known to directly affect several cellular processes by effects on ion channels or gene expression (Bunn and Poyton, 1996). These effects can be triggered by environmental hypoxia or cardiopulmonary disease that results in arterial or tissue hypoxia. The effects on ion channels are rapid so any memory-like effects of IH are secondary effects. For example, depolarization affects gene expression independent of changes in PO_2. A direct effect of hypoxia on gene expression is exerted by hypoxia inducible transcription factor (HIF-1) that occurs in every cell type studied in response to hypoxia (Bunn and Poyton, 1996). HIF-1 is regulated at the post-transcriptional level by proteasomes, which degrade the HIF-1α subunit in the presence of oxygen. HIF-1 was originally described as the promoter for erythropoietin transcription, which is a hallmark of the response to CH. Subsequently, HIF-1 has been shown to have many other physiologically relevant effects in hypoxia such as stimulating expression of transferrin, several glycolytic enzymes and angiogenesis through vascular endothelial growth factor (VEGF) (Bunn and Poyton, 1996).

HIF-1 is likely involved in signaling the effects of IH as well as CH in many physiological systems and this is being studied in some interesting *in vitro* systems. For example, CH blunts the hypoxic VEGF response in cultured heart and liver cells (Levy, 1999). When these cells are returned to normoxia following 48–72 h of CH, they show less of an increase in VEGF with acute hypoxia compared to control normoxic cells. A similar phenomenon is observed for HIF-1 when cultured neurons are exposed to IH (Ruscher et al., 1998). The increase in HIF-1 with an acute hypoxic challenge is significantly blunted by 1 h of exposure to hypoxia 48 h prior to the acute challenge. These results suggest that the effects of IH and CH may be similar on the HIF-1-mediated angiogenic response in the heart and brain. These results have important implications for heart attack and stroke and demonstrate the potential value of such simple model systems for understanding fundamental mechanisms of IH compared to other patterns of hypoxic exposure.

Future research directions

The fundamental problem in this field remains determining the physiological mechanisms for differences in responses to IH versus CH or acute hypoxia. A first step in answering this question could be investigating the concept of a "dose" of hypoxia. The effects of exposure to different patterns of hypoxia with the same total duration need to be compared. Exposures to different levels of hypoxia should also be studied (e.g., comparing ten 2-h exposures to hypoxia producing $SaO_2 = 85\%$ and ten 1-h exposures to $SaO_2 = 70\%$). Molecular biological studies and *in vitro* cellular systems could be used to determine if thresholds exist for specific mechanisms.

The effects of IH in intact organisms could differ greatly from reduced preparations, however, because of the interaction of multiple systems. We focused on ventilation and erythropoiesis, but the interactions of fluid and acid-base balance may be important in explaining differences between IH and CH also. For example, the complex control of plasma volume responds rapidly to hypoxia and the response changes with time during CH (Milledge, 2000). It remains to be determined which specific mechanisms controlling plasma volume change during IH. The interaction between fluid and acid-base balance may determine physiological responses to IH also. For example, the kidney is slow to correct an alkalosis in the presence of volume depletion and this may delay the metabolic compensation for respiratory alkalosis at extreme altitude (Milledge, 2000). If IH caused ventilatory acclimatization without a decrease in plasma volume, then acid-base compensation might occur faster with IH than with CH, and alter the response to a given dose of hypoxia.

The fact that these interactions are complex argues for "whole animal" studies. However, caution must be exercised when extrapolating between species, just as in extrapolating from *in vitro* to *in vivo* studies. For example, the renal mechanism proposed to explain the slow metabolic compensation for a respiratory alkalosis in rats is different than that proposed for humans (Milledge, 2000). Also, in contrast to human studies of IH (see above), rats show polycythemia (and right ventricular hypertrophy) with IH (e.g., after 28 days of 2-h exposures to 10–12% O_2 at sea level; Nattie and Doble, 1984; Moore-Gillon and Cameron, 1985). Hence, human studies or experiments designed specifically to test the relevance of animal models to humans may be necessary to understand IH in humans.

Genetic approaches are promising for understanding species differences and discovering new physiological mechanisms that might not be predicted from our current understanding of IH. For example, a polymorphism of the human angiotensin converting enzyme (ACE) gene has been described recently in which the deletion (D) rather than the insertion (I) allele is associated with higher activity of tissue ACE. Although evidence for a skeletal muscle renin-angiotensin system suggested that the D allele should be associated with better physical performance, Montgomery et al. (1999) showed that performance in high altitude mountaineering is significantly associated with the I allele. The authors conclude that this might be explained by a number of physiological mechanisms, including many not involved in O_2 transport directly. The potential for studying genome-wide patterns of expression with microarrays should help identify the physiological mechanisms of the ACE(I) genotype advantage at altitude. The same experimental design and tools can be used to determine if there is a genetic basis for the response to IH and differences in the physiological mechanisms evoked by IH versus CH.

IH IN NATURE

Considering the problem of IH in general in natural has at least two benefits. First, a comparative approach may identify species that are ideal to study the problem of IH. Second, a comparative approach can help define the evolutionary origins of physiological responses to IH and this improves our understanding of physiological mechanisms and ability to apply these mechanisms. For example, a blunted angiogenic response following IH may represent an ancestral condition appropriate for cold-blooded animals, and small mammals, that generally decrease metabolism (i.e., O_2 demand) in response to decreased O_2 supply (Mortola and Gautier, 1995).

An interesting case in nature from this point of view is IH in the primordial conditions of aquatic systems. Graham (1997) has considered the evolution of air-breathing fish as a response to different patterns of IH. The oxygen environment in aquatic systems can undergo huge daily variations, ranging from atmospheric PO_2 to anoxia, as O_2 is produced by photosynthesis during the day and consumed by respiration at night. Fish in the intertidal zone are also subject to large variations in PO_2 in the burrows they use to wait out receding waters. Progressive continuous hypoxia has been studied in such animal models (Ishimatsu et al., 1999), but

IH has not. There is already rich literature on the comparative physiology of acute and chronic hypoxia (Tenney and Leiter, 1995). Studying IH in such aquatic models, as well as in animals migrating at high altitude, burrowing or diving, may be a fruitful area for future research.

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