

Physiological Responses to Intermittent Hypoxia in Humans

by

Jon C. Kolb

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**PHYSIOLOGICAL RESPONSES
TO INTERMITTENT HYPOXIA IN HUMANS**

By

Jon C. Kolb

A Thesis

**Submitted to the Institute for the Theory and Practice of Training
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CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

Hypoxia is a general reduction in oxygen delivery, either because of decreased arterial oxygen content, decreased cardiac output, or decreased oxygen uptake in the systemic capillaries, which may result from a multitude of medical complications, environmental factors, or physical exertion. The complex physiologic and symptomatic adaptations to hypoxia have been extensively investigated during the past century (Bert, 1878; FitzGerald, 1914; Pugh, 1964; Roach and Hackett, 2001; Basnyat and Murdoch, 2003). Interest in the effects of hypoxia is of clinical importance in determining the pathophysiology of cerebrovascular diseases (Schoene, 1999; Segler, 2001; Severinghaus, 2001) and cardiopulmonary diseases (Neubauer, 2001; Morgan and Joyner, 2002; Serebrovskaya, 2002). Furthermore, understanding the adaptive changes which occur during high altitude sojourns is physiologically relevant in discerning the etiology of diseases such as acute mountain sickness and high altitude cerebral edema (Hackett et al., 1998). From an applied point of view, sport physiologists have for many years investigated the potential ergogenic benefits of altitude training and subsequent improvement in athletic performance (Buskirk et al., 1967; Faulkner et al., 1967; Wilbur, 2001; Levine, 2002).

1.1.1 Acclimatization to Hypoxia

Acclimatization to chronic hypoxia follows a time dependent continuum (minutes, days, weeks) which progresses through increased ventilation, alterations in

cerebrovascular and cardiovascular dynamics, and subsequently metabolic changes at the tissue level which reciprocally function to enhance oxygen extraction and utilization (Hackett, 2002). Acute hypoxia is detected by the carotid bodies located close to the bifurcation of the common carotid artery. The high rate of perfusion in the carotid body combined with its' sensitivity to a reduction in the partial pressure of oxygen, activates afferent impulses to the respiratory center of the medulla stimulating an increase in pulmonary ventilation (Dempsey and Forster, 1982; Smith et al., 1986; Lahiri et al., 2000). Hypocapnia and respiratory alkalosis occur secondary following this hypoxic-induced ventilatory stimuli (Moore et al., 1986; Weil, 1986). While hypocapnia alone normally results in cerebral vasoconstriction, the effect is significantly offset by reduced oxygen delivery to the brain at altitude, resulting in a net decline in cerebral vascular resistance and a reciprocal increase in cerebral blood flow (Otis et al., 1989; Krasney, 1994; Buck et al., 1998; Jansen et al., 1999; Severinghaus, 2001).

Similarly, increased heart rate, reduced plasma volume, and elevated hematocrit work synergistically to optimize the circulatory function assisting oxygenation at the tissue level. Erythropoietin, released from the hypoxic kidney, increases red blood cell mass overtime further enhancing oxygen delivery to the cell in an attempt to regain homeostasis (Milledge and Cotes, 1985; Eckardt et al., 1989). With respect to high altitude physiology and the numerous ventilatory and

hematological changes associated with hypoxic stress, several authors have reported a relationship between the degree of hypoxemia and the onset of acute mountain sickness (AMS) (Roach et al., 1998; Saito et al., 1999; Hussain et al., 2001; Kolb et al., 2001). Symptoms associated with AMS include headache, lethargy, fatigue, peripheral edema, and loss of appetite (Singh et al., 1969; Hackett and Rennie, 1976). The pathology of AMS follows a complex symptomatic continuum, the severity of which is dependent on altitude gained, rate of ascent, prior acclimatization, and the individual's susceptibility to the effects of lowered arterial oxygen concentration (Lyons et al., 1995; Powell and Garcia, 2000; Roach and Hackett, 2001).

Although the physiological responses to hypoxia are extensive, this dissertation focuses specifically on alterations in both respiratory control and cerebrovascular responses. Vasomotor reactivity to acute hypoxia has been suggested by several authors to trigger cerebral vasodilation and hence cerebral blood flow (CBF), which may in turn initiate the clinical symptoms of AMS (Krasney, 1994; Jansen et al., 1999; Schoene, 1999). If the hypoxic stress is severe and continuous, cerebral edema may develop, and in some individuals may progress to high altitude cerebral edema (HACE) characterized by ataxia and altered levels of consciousness (Hackett, 1999a).

A recent review of cerebral circulation at high altitude (Severinghaus, 2001) identified that individual variability in the magnitude of cerebral blood flow changes in response to hypoxia depends on the integrated drive of four reflexive mechanisms:

- i. The acute ventilatory response to hypoxia (AHVR).
- ii. The acute ventilatory response to increased arterial carbon dioxide (AHCVR).
- iii. The cerebral vasodilative response to hypoxia.
- iv. The cerebral vasoconstrictive response associated with hypocapnia.

The array of complex interactions between ventilatory and cerebrovascular systems during periods of reduced oxygenation has potential implications on virtually all major physiological systems. Therefore the remainder of this chapter considers specific alterations in AHVR, AHCVR, and the cerebrovascular responses to hypoxemia.

1.1.2 Ventilatory Acclimatization to Hypoxia

The sensitivity of the carotid bodies to reductions in arterial oxygen pressure (PaO_2) governs the extent to which AHVR is augmented (Smith et al., 1986). An increase in the AHVR allows ventilatory acclimatization to proceed, despite respiratory alkalosis and a withdrawal of the stimulus to the peripheral chemoreceptors (Dempsey and Forster, 1982). Similarly an increase in the

AHCVR occurs during chronic hypoxia as the central chemoreceptors respond to reduced end-tidal P_{CO_2} (Cunningham et al., 1986).

As a diagnostic tool, AHVR by definition is an assessment of an individual's ventilatory sensitivity to progressive isocapnic hypoxia (Ward et al., 2000). Historically, methods for measuring ventilatory sensitivities to hypoxia have included brief exposures (five to ten minutes) of progressively reduced inspiratory oxygen content (Weil et al., 1970) or re-breathing methods that generate a hypoxic stimulus (Rebuck and Campbell, 1974) in which the end tidal carbon dioxide pressure (P_{ETCO_2}) is held constant (isocapnic). The isocapnic control throughout the test is important to isolate the ventilatory drive associated with hypoxia, which would otherwise be masked by the reduction in CO_2 as a result of hyperventilation and therefore reduce the stimulus to breath (Grover, 1994). Both methods (Weil et al., 1970; Rebuck and Campbell, 1974) quantify AHVR by comparing ventilation to end tidal oxygen pressure (P_{ETO_2}). More recently, progressive isocapnic hypoxic protocols have been used to describe AHVR by comparing the ratio of changes in ventilation with changes in SaO_2 (Mou et al., 1995; Katayama et al., 1999). Alternatively, a series of square wave pulses of hypoxia, where carbon dioxide levels were fixed at the subjects resting level, has been utilized in accurately quantifying AHVR through a mathematical fitting model that incorporates both peripheral and central chemoreflexes (Howard and Robbins, 1995). The model developed by a group from the University of Oxford,

describes parameter G_p (hypoxic sensitivity), which represents the change in ventilation for a given change in SaO_2 .

Regardless of the methodology used, several investigators have reported that AHVR increases following relatively short (eight hours) exposures to hypoxia (Howard and Robbins, 1995; Fatemian et al., 2001) days or weeks of hypoxia (Schoene et al., 1990; Tansley et al., 1998), and that elevated ventilatory responses to hypoxia may persist for up to a week following hypoxic conditioning (Katayama et al., 1999). As such, the increases in AHVR which arises from hypoxia elevates SaO_2 improving oxygenation, and therefore has been identified as a cornerstone of ventilatory acclimatization (Casas et al., 2000). However, between-individual AHVR variation is great, and a blunted HVR may contribute to the susceptibility of AMS via attenuation of the arterial oxygen content (Schoene, 1982; Moore et al., 1986; Matsuzawa et al., 1989; Casas et al., 2000; Bartsch et al., 2001).

1.1.3 Cerebrovascular Responses to Hypoxia

1.1.3.1 Cerebral Blood Flow

Over fifty years ago reduced inspired oxygen fraction ($F_I O_2 = 0.10$) was reported to result in an SaO_2 of 65% in humans, while cerebral blood flow (CBF) determined from N_2O uptake by the brain, exhibited an increase of 35% when compared to resting ventilation under normoxic conditions (Kety and Schmidt, 1948). The first measurement of human CBF response to high altitude (3810m)

using the methodology of Kety and Schmidt (Kety and Schmidt, 1945) indicated a 24% increase over sea level values (Severinghaus et al., 1966). More recently, the non-invasive technique of transcranial Doppler ultrasonography (TCD) has been employed for the accurate evaluation of cerebral blood flow in response to acute variations in O₂ and CO₂ (Poulin et al., 1996; Poulin et al., 2002).

Using TCD to determine the velocity of cerebral blood flow (CBFv), stepwise acute isocapnic hypoxia (SaO₂ \cong 90, 80, 70, 60%) resulted in a 35% increase in normal human subjects residing at sea level (Jensen et al., 1996). Interestingly, after five days of altitude acclimatization (3810m), the same subjects exhibited a 46% increase in CBFv to the stepwise isocapnic hypoxia test, thus indicating an increased cerebral vasoreactivity following five days of continuous hypoxia. Jensen and colleagues (1996) identified a hyperbolic association between CBFv and SaO₂, similar in shape to AHVR.

Middle cerebral artery velocity (MCAv) was measured in climbers ascending to high altitude to assess the relationship between CBF regulation and the onset of AMS (Otis et al., 1989). Using TCD, a significant increase in MCAv was noted between sea level control values and measurements obtained at 4115m (55 ± 7 and 71 ± 13 cm/sec respectively). Otis and colleagues (1989) suggested that the increased CBF in theory may contribute to the pathophysiology of AMS and HACE due to a transcranial leakage from increased arterial blood pressure resulting in cerebral edema and increased intracranial pressure leading to

displacement and stretching of the pain sensitive trigeminovascular structures. This 'vasogenic theory', associated with high altitude headache, AMS, and HACE has since been supported by several research groups (Krasney, 1994; Buck et al., 1998; Hackett, 1999b; Sanchez del Rio and Moskowitz, 1999).

Similarly, following 72 hours at an elevation of 4559m, MCAv (quantified by TCD) and blood gas analysis of arterial PO₂ were measured in concert with self reported AMS symptomatology in 23 healthy males (Baumgartner et al., 1994). The mean cerebral blood velocity increased 148 ± 16% over sea level values in subjects reporting AMS, while the increase was 127 ± 24% in subjects without AMS. Baumgartner and colleagues (1994) also identified that MCAv exhibited a significant negative correlation ($r = -0.51$, $p < 0.001$) with arterial PO₂ throughout the high altitude exposure.

Further evidence that increased cerebral vasomotor reactivity contributes to the development of AMS has been described in high altitude trekkers reaching Pheriche (4243m) en route to Mount Everest Base Camp (Jansen et al., 1999). The Lake Louise AMS scoring system questionnaire (Roach et al., 1993) was employed to classify the climbers into two groups: those presenting with AMS symptoms and subjects reporting no AMS. Data collected by Jansen's group (1999) included TCD quantification of MCAv, SaO₂, and transcutaneous PCO₂. While PCO₂ levels were essentially the same, subjects exhibiting AMS symptoms

had higher resting cerebral blood velocity than did no AMS subjects (74 ± 22 and 56 ± 14 cm/s respectively). Additionally, SaO_2 was significantly lower in AMS subjects compared to no AMS subjects ($80 \pm 8\%$ and $88 \pm 3\%$ respectively).

1.1.3.2 Cerebral Oxygenation

The non-invasive assessment of cerebral oxygenation with near infrared spectroscopy was first described in 1991 (McCormick et al., 1991) as a new monitoring index to estimate cerebral regional oxygen saturation (S_rO_2).

Method comparison validation studies have illustrated the accuracy of cerebral oximetry (Grubhofer et al., 1999; Kim et al., 2000; Shah et al., 2000) while a number of publications have identified various clinical applications (Blas et al., 1999; Higami et al., 1999; Yao et al., 2001) as well as the utility in determining exercise intensity in humans (Nielsen et al., 1999; Saito et al., 1999).

Cerebral oximetry has also been employed to assess the oxygen status of the brain during sojourns to high altitude (Imray et al., 1998). Sea level cerebral oxygenation measurements were made on male (17) and female (3) volunteers with a Critikon 2020 cerebral oximeter (Johnson and Johnson Medical Ltd., UK) and following rapid ascent by automobile to 2270, 3650, and 4680m on consecutive days. In this, the first reported investigation monitoring cerebral oxygenation in the field at altitude, Imray and colleagues (1998) reported a parallel decline in both SaO_2 and S_rO_2 , while AMS symptoms, diagnosed with the

Lake Louise AMS scoring system questionnaire (Roach et al., 1993), were more severe as SrO_2 fell ($r = -0.41$, $p >0.05 < 0.1$). As well, cerebral deoxygenation has been observed in unacclimatized trekkers at altitude (4300m) (Saito et al., 1999). Saito and colleagues (1999) suggest that the acute reduction in S_iO_2 , followed by increased CBF, might be a primary cause of headache and AMS. Thus, the non-invasive monitoring of cerebral oxygenation is likely to be of critical importance in determining physiologic and symptomatic function at high altitude.

1.1.4 Intermittent Hypoxia

While much is known about the physiological responses to acute and chronic hypoxic exposures, far less is known about the effects of intermittent hypoxia (Powell and Garcia, 2000; Schmidt, 2002). Intermittent hypoxia, also referred to as discontinuous hypoxia, has been defined as repeated exposures to hypoxia, which are separated by periods of normoxia, or by episodes of hypoxia that are less severe (Powell and Garcia, 2000; Neubauer, 2001). Intermittent hypoxic protocols utilized with human subjects have varied greatly with respect to the total time frame of episodic cycles, the severity of hypoxia, and the number of hypoxic cycles per day. Relatively short protocols have varied from those that examined alternating between five minutes of hypoxia (simulated altitude of 6,000m) and five minutes of normoxia over sixty minutes twice per day for sixty days (Hellemans, 1999), to protocols which investigated ninety minutes of hypoxia (simulated altitudes of 4000m and 5500m) three times per week for 3 weeks

(Rodriguez et al., 2000). Extended discontinuous hypoxic protocols have incorporated eight to ten hours of overnight hypoxia for twenty-one days (Townsend et al., 2002) or longer cycles (twelve to sixteen hours per day) of hypoxia (simulated altitude, 2500m) over a twenty-five day period (Rusko et al., 1999). Irrespective of the protocol design, these repeated hypoxic episodes separated by periods of normoxia, have elicited changes in respiratory control (Rodriguez et al., 2000; Townsend et al., 2002) and hematogenesis (Hellemans, 1999; Rodriguez et al., 2000; Townsend et al., 2002), suggesting that there may be a cumulative effect of intermittent hypoxic episodes (Neubauer, 2001). Whether or not similar mechanisms are responsible for the physiological adaptations to discontinuous bouts of hypoxia are the same as those observed during chronic hypoxia, remains to be established (Powell and Garcia, 2000).

Recently, endurance athletes and high altitude climbers have gained access to commercially available, portable normobaric hypoxic chambers. Intermittent exposures to hypoxia in these chambers may elicit adaptations similar to those observed during acclimatization to altitude (Wilbur, 2001; Schmidt, 2002). Manufactures of these systems purport that intermittent exposures may elicit adaptations similar to those observed in response to the hypoxia of high altitude, however there have been no reports in the scientific literature that ventilatory acclimatization or alterations in cerebrovascular dynamics occur following repeated episodes in the portable chambers.

Thus, the goal of this dissertation is to provide a detailed investigation into the physiologic and symptomatic responses following an intervention of discontinuous normobaric hypoxia, which employs portable chambers. To accomplish this, an intermittent protocol was developed which cycled between 8 hrs of nocturnal hypoxia at a simulated altitude of 4300m, followed by 16 hrs of normoxia, for five consecutive days. Specifically, it is not currently known if cerebrovascular and ventilatory sensitivities to acute hypoxia are altered, or if altitude-like symptoms develop, in response to such an intermittent hypoxic protocol. This understanding will contribute to the emerging body of knowledge concerning dose-response effects owing to intermittent hypoxia, in determining whether the responses elicit protective adaptations, or cross over the dosage threshold, resulting in pathological disorders.

1.2 OBJECTIVES OF THESIS

Using normobaric hypoxia to elicit various levels of hypoxemia in humans, the following objectives are outlined to show the logical progression of experiments designed to engender a better understanding of changes in respiratory control and cerebrovascular dynamics following intermittent hypoxia:

- 1) Determine the validity of pulse oximetry in monitoring the state of arterial oxygenation during progressive normobaric hypoxia.

- 2) Develop a protocol for quantifying the cerebrovascular and ventilatory responses to acute variations in oxygen and carbon dioxide.

- 3) Design and implement a discontinuous hypoxic intervention to determine the extent and time frame for the development, and reversibility, of physiological and symptomatic perturbations.

It is envisaged that accomplishing these objectives will lead to a greater understanding of the dose-response effect of discontinuous hypoxia, and will provide insight regarding the basic efficacy of intermittent hypoxia. Specific aims and hypotheses are outlined in each respective chapter.

1.3 STRUCTURE OF THESIS AND PRESENTATION

The studies within the thesis are separated into four distinct phases, which were conducted sequentially. This sequential construction of the thesis was necessary because the results of each phase helped to finalize the research protocol for each subsequent investigation. Presentation of the dissertation is carried out as follows: Chapters 2, 3, 4, and 5 are based on manuscripts that have been accepted