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PERSISTENCE OF INTERMITTENT HYPOXIA EXPOSURE ACCLIMATION TO
SIMULATED HIGH ALTITUDE

A thesis submitted in partial fulfillment of the requirement for Departmental Honors
in Interdisciplinary Studies at
The College of William and Mary in Virginia

by

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Abstract

This study investigated the persistence of adaptation to intermittent normobaric hypoxic exposures (IHE) of three hours each day for three consecutive days to a sea-level barometric pressure atmosphere with an oxygen fraction simulating the partial pressure of oxygen found at 4,300 m altitude. End-tidal CO₂ (PEtCO₂), Acute Mountain Sickness scores (AMS-C), Heart Rate (HR), Blood Oxygen Saturation (SaO₂) and Mood State were measured before and after all exposures to this simulated 4,300 m altitude.

PEtCO₂, the hallmark of adaptation to high altitude, was reduced after the three days of acclimation and remained reduced after 24 hours but returned to control values by 48 hours post IHE.

The results of this study suggest that decay of IHE acclimation to a simulated altitude of 4,300 m is substantially complete between 24 and 48 hours after the last three hour exposure to a simulated altitude of 4,300 m.

Persistence of Intermittent Hypoxia Exposure Acclimation to Simulated High Altitude

Due to modern transportation and lifestyle changes, exposure to high altitudes occurs more frequently today than ever before, a trend known as the lowlander sojourn to high altitude (Honigman et al., 1993; Maggiorini, Bühler, Walter and Oelz, 1990). When humans ascend to altitudes greater than 2,500 m their bodies must adapt to the adverse atmospheric conditions before they are able to function close to sea-level capacity. This adaptive process, known as acclimatization, describes how the body neutralizes the adverse effects of hypobaric hypoxia and depends strongly on individual variability, the rate of ascent and the degree of elevation (Burstcher Szubski, 2008; Dean et al., 1990; Honigman et al., 1993; Maggiorini et al., 1990).

Hypobaric hypoxia describes the low-pressure, low-oxygen conditions that distinguish high altitude from sea-level. Hypobaric connotes atmospheric pressure below the standard sea-level pressure of 760 mmHg. For reference, the 5,350 m base camp of Mt. Everest has a barometric pressure of approximately 390 mmHg while the 8,848 m summit has one of 253 mmHg (Cerretelli, 1976; Gallagher and Hackett, 2004; Sutton et al., 1988). The proportion of oxygen in air remains constant at 20.9% up to altitudes near 12,000 m, but the progressive loss of barometric pressure with increasing altitude yields a decrease in ambient oxygen pressure (Sutton et al., 1988; Virués-Ortega, Buéla-Casal, Garrido and Alcázar, 2004). This reduction of oxygen available for respiration at high altitude is known as hypoxia. As a result, at altitudes above 2,500 m most people experience a decrease in arterial saturation of oxygen (SaO_2) known as hypoxemia, or

low blood oxygenation, which induces symptoms of acute mountain sickness (AMS) (Moore, 2000; Honigman et al., 1993; Maggiorini et al., 1990).

Acute mountain sickness is characterized by such symptoms as headache, nausea and general malaise, and frequently debilitates unacclimatized individuals (Honigman et al., 1993; Maggiorini et al., 1990; Roach et al., 1996). Recent research also indicates a relationship between altitude, AMS and negative alterations in mood state (Shukitt and Banderet, 1988; Shukitt-Hale, 1991; Shukitt-Hale et al., 1998). The lowlander sojourn to high altitude is usually extremely rapid and does not allow sufficient time for progressive acclimatization, increasing the incidence and severity of AMS in people newly exposed to high elevations (Maggiorini et al., 1990). A gradual ascent allows sojourners to high altitude to avoid extreme and debilitating AMS through progressive incremental acclimatization. If an individual afflicted with AMS halts further ascent and rests at the current altitude, AMS symptoms generally resolve within 2 to 7 days as the body acclimatizes, allowing the sojourner to proceed to higher elevations with minimal impairment (Fulco, Rock and Cymerman, 1998). To minimize the incidence of AMS, an individual's ascent should not exceed the time course of acclimatization which is approximately 300 to 600 m per day at altitudes above 2,000 m (Hackett and Roach, 2001; Muza, 2007; Purkayastha et al., 1995; Schneider et al., 2002). With adequate time at altitude the body compensates for the adverse hypoxic conditions and most AMS symptoms recede to sub-clinical levels or resolve completely. Planes and cars, however, enable people to travel from sea-level to extreme altitudes in a matter of hours. This manner of ascent increases the risk and severity of suffering from the deleterious effects of high altitude exposure.

Given the increase in lowlanders traveling to high altitudes and suffering from AMS, there is great interest in reproducing acclimatization in a controlled laboratory setting (Burtsher, 2008; Levine, 2002). By mimicking high altitude conditions researchers at sea-level can study altitude physiology through periodic exposure to hypoxia, known as Intermittent Hypoxia Exposure (IHE). Physiological adaptation to simulated altitude is known as acclimation. Recreating the critical elements of high altitude by manipulating IHE in the laboratory attempts to “bring the mountain to the mountaineer”, so to speak, to facilitate controlled research on altitude acclimation physiology (Levine, 2002). Researchers replicate altitude hypoxia in two ways: by decreasing barometric pressure to produce hypobaric hypoxia, or by decreasing the oxygen fraction of ambient air to yield normobaric hypoxia, or sea-level pressure hypoxia (Levine, 2002; Savourey et al., 2003). There is widespread interest in successfully replicating high altitudes in the laboratory to stimulate the physiological adjustments of acclimatization that could benefit the sojourner at altitude (Burtscher, Brandstätter and Gatterer, 2008; Burtscher, Szubiski and Faulhaber, 2008; Gore, Clark, and Saunders, 2007; Levine et al., 1991; Levine, 2002; McClean, 2005; Muza, 2007; Richardson, Lodin, Reimers and Schagatay, 2007; Rodríguez et al., 1999).

For lowlanders planning to ascend to high altitude, pre-acclimation in simulated altitude environments prior to ascent has important physiological and health implications. Once at altitude a pre-acclimated individual may experience attenuated neuropsychological symptoms and AMS symptoms, benefits that extend to mountain climbers, high altitude vacationers, and to military personnel faced with rapid deployment to extreme altitudes (Burtscher et al., 2008; Burtscher et al., 2008; Honigman

et al., 1993; Maggiorini et al.; 1990; Muza, 2007). In addition to the physiological consequences of AMS, unacclimatized individuals at altitude also experience a decrease in aerobic performance, implying that more energy must be exerted to perform tasks that would be less taxing at sea-level (Fulco et al., 1998; Muza, 2007; Pugh et al., 1963). In order to understand the benefits that may be gained through controlled IHE, researchers continue to seek a thorough understanding of the mechanisms that contribute to acclimation and acclimatization.

The physiological effects of hypoxia, such as the hypoxic ventilatory response, are evident within the first hours of exposure and the onset of AMS is usually seen within the first 4 to 24 hours (Levine, 2002; Muza, 2007). If symptoms do not progress into more advanced and life-threatening conditions, the debilitating effects of altitude generally recede within 3 to 5 days (Muza, 2007). What remains unclear, however, is the persistence of this acclimatization once the body has successfully adjusted to high altitude. If it is indeed possible to simulate the key elements of altitude and effectively pre-acclimate individuals, it is important to know under what conditions acclimation can be achieved and how long it will persist after controlled exposure. The purpose of this study is to measure the indicators of acclimation to normobaric IHE of 3 hours per day at 4,300 m, and at 24 and 48 hours post IHE in order to determine the rate of decay of IHE acclimation.

Acute Mountain Sickness

Acute Mountain Sickness is a syndrome that commonly occurs in humans at high altitude, especially with rapid ascent (Hackett and Roach, 2001; Virués-Ortega, 2004). Symptoms that indicate AMS include headache, insomnia, ataxia and gastrointestinal disturbances including nausea, anorexia and vomiting. Headache and one or more additional symptoms is sufficient for a diagnosis of AMS and symptoms generally emerge within 6 to 10 hours, though it can be in as little as 1 hour. Symptoms vary in incidence and severity depending on the rate of ascent, the level of altitude, and individual susceptibility, and can be considerably debilitating even when mild (Burtscher et al., 2008; Hackett and Roach, 2001; Maggiorini et al., 1990; Roach, Loeppky and Icenogle, 1996). If the rate of ascent exceeds the individual's ability to acclimatize, the body can not compensate for the decrease in available oxygen and the individual will experience more pronounced hypoxemia (Virués-Ortega et al., 2004). This is especially dangerous at extreme altitudes near 8,000 m where the scarcity of ambient oxygen due to decreased atmospheric pressure increases the likelihood of life-threatening end-stage AMS (Gallagher and Hackett, 2004; Hackett and Roach, 2001; Sutton, 1998; Virués-Ortega et al., 2004). If complications do not arise, however, AMS is most often self-limiting and resolves within 3 to 5 days as the body acclimatizes (Muza, 2007).

The exact pathogenesis of AMS is not completely understood, but it is considered an altitude-induced cerebral abnormality that can be fatal in its advanced stage, known as High Altitude Cerebral Edema, or HACE (Gallagher and Hackett, 2004; Hackett and Roach, 2001). At rest the brain consumes roughly 20% of the total oxygen in the body to fuel neurological functioning and is therefore extremely sensitive to hypoxemia. When

exposed to hypoxic conditions, all humans display some swelling of the brain as the body adjusts cerebral blood flow (CBF) to optimize oxygen delivery (Gallagher and Hackett, 2004; Hackett and Roach, 2001; Naije and Osta, 2007). In their 2007 research review of altered autoregulation of CBF in hypoxia, Naije and Van Osta affirm that brain edema in humans at high altitudes is a reliable determinant of both AMS and HACE. In a state of hypoxia cerebral blood vessels maintain sufficient oxygenating blood flow through vasodilatation. Research suggests that the resulting elevation in CBF is significant in the pathophysiology of AMS. Naeije and Van Osta (2007) suggest that rather than the specific CBF changes, the hypoxia-induced impairment of CBF autoregulation may be a determining mechanism in AMS development (Naije and Osta, 2007). There is also significant evidence that exposure to high altitude negatively affects neuropsychological functioning, though it is not clear if cognitive impairment is dependent on the presence of AMS (Virués-Ortega et al., 2004). Kramer, Coyne and Strayer (1993) find no correlation between severity of AMS and reduction in reaction time in 20 climbers ascending to 2,195 m compared to a sea level control, though the researchers did observe sustained deficits in learning and memory tasks 1 to 2 weeks after the climb (Kramer et al., 1993).

As millions of people travel to high altitudes every year the rising occurrence of AMS has become a significant public health problem (Hackett and Roach, 2001). In a study of the incidence of AMS in conference attendees in the Rocky Mountain foothills (1,920 m to 2,957 m), Honigman et al. (1993) find that 25% of participants (n=3,158) displayed symptoms, most within 12 hours of first exposure (Honigman et al., 1993). Maggiorini, Bühler, Walter and Oelz (1990) report concurring results in the incidence of AMS in climbers in the Swiss Alps, noting a strong correlation between incidence and

altitude: 9% at 2,850 m, 13% at 3050 m, 34% at 3,650 m and 53% at 4,559 m (Maggiorini et al., 1990). This pattern is supported by studies that note a similar increase in incidence with rapid ascent and higher altitudes (Dean et al., 1990; Montgomery, Mills and Luce, 1989; Schneider, Bernasch, Weymann, Holle and Bärtsch, 2002).

Schneider et al. (2002) further examine the established risk factors involved in AMS in 827 subjects at 4,559 m. Researchers divided the sample population into susceptible and non-susceptible groups based on a history of AMS symptoms. Subjects completed an AMS questionnaire on the day of arrival to altitude as well as the following morning. Results indicate a clear pattern of risk factors correlated to the occurrence of AMS (as determined by the Environmental Symptoms Questionnaire): in the susceptible group, 58% of subjects with rapid ascent but without exposure to altitude in the past two months were classified as having AMS. In subjects with both rapid ascent and prior exposure, 29% reported AMS. Among subjects with a slow ascent but no previous exposure, 33% indicated AMS. The lowest rate of AMS occurrence was 7%, observed in subjects who had both a slow ascent and a previous exposure. The non-susceptible group mirrored this pattern with 31%, 16%, 11% and 4%, respectively (Schneider et al., 2002).

The results of the Schneider et al. (2002) study clearly indicate that individual susceptibility, rate of ascent, and pre-exposure are primary and independent determinants of AMS, just as Maggiorini et al. (1990) and other studies clearly demonstrate the significance of degree of altitude (Dean et al., 1990; Honigman et al., 1993; Maggiorini et al., 1990; Montgomery et al. 1989; Schneider et al., 2002). With a limited understanding of the mechanisms of individual susceptibility, researchers continue to focus on attenuating the effects of AMS through simulated gradual ascent and pre-exposure to

IHE-simulated altitude. A 2008 review by Burtcher, Brandstätter and Gatterer observes that few studies have been completed that evaluate the acclimatizing effects of intermittent hypoxia exposure, and there is no standard exposure protocol between experiments, making it difficult to assess possible benefits of IHE (Burtcher et al., 2008). The researchers conclude from their review that 1 to 4 hours of IHE exposure per day for 1 to 5 weeks at approximately 4,000 m prompts some adaptations to high altitude that may be beneficial in pre-acclimation. According to Burtcher et al. no conclusive statements can be made about the effectiveness of simulated altitude exposure to reduce the incidence of AMS. Grant et al. (2002) find a poor correlation between AMS scores and physiological variables in normobaric hypoxia compared to measurements at comparable altitudes in the Himalayan Mountains (Grant et al., 2002). Beidleman et al. (2004), however, determine that 3 weeks of IHE for 4 hours per day, 5 days per week at a simulated altitude of 4,300 m is sufficient to provide an alternative to extended exposure to altitude to reduce incidence and severity of AMS. The researchers also observe that the reduction in AMS is inversely related to the increase in oxygen saturation of SaO₂ (Beidleman, 2004).

Though most studies to date have been inconclusive, it is evident that some degree of acclimation can be attained through IHE-simulated high altitudes. Research on IHE-simulated altitude, especially regarding normobaric hypoxia, is a relatively new field of study, and much more research must be completed before definitive patterns can be established. Given the potential benefits of controlled acclimation, laboratory IHE may be valuable to high altitude sojourners seeking to attenuate AMS symptoms through pre-acclimation (Burtcher et al., 2008; Maggiorini et al., 1990; Roach et al., 1996).

Mood State Alterations

Within the past two decades researchers have begun to investigate the significance of altitude-induced mood alterations and the observed correlation to severity of AMS (Shukitt and Banderet, 1988). Shukitt and Banderet (1988) compare self-reported mood states at two different altitudes, 1,600 m and 4,300 m, in 25 male and female subjects, finding that friendliness, clear thinking, dizziness, sleepiness and unhappiness are affected at 4,300 m, while only sleepiness is affected at 1,600 m (Shukitt and Banderet, 1988). The results also indicate a specific time-course of mood state alteration at 4,300 m as mood differed from baseline scores upon initial ascent (1-4 hours after arrival), increased in severity after 1 day (18-28 hours) and returned to baseline levels by day 2 (42-52 hours) (Shukitt and Banderet, 1988). Shukitt-Hale, Rauch and Foutch (1990) assess changes in AMS symptoms and mood state during an ascent to 3,630 m to further clarify the impact of degree of altitude, rate of ascent, length of stay and expended effort on these self-reported changes (Shukitt-Hale, Rauch and Foutch 1990). Shukitt-Hale and colleagues again find that adverse changes in symptoms and mood increase with altitude, and suggest that other factors such as effort and temperature would also influence the observed changes (Shukitt-Hale et al., 1990). Weather, temperature and physical exertion may not be present in a controlled, simulated altitude study in a hypoxic chamber. Hypobaric hypoxia has, however, been shown to be sufficient to induce negative effects on mood state that are further aggravated by rapid ascent and increasing simulated altitude (Crowley et al., 1992; Shukitt-Hale, Banderet and Lieberman, 1998; Li et al., 2000).

The time-course of mood state alterations and their increasing severity at higher altitudes reflect those AMS patterns observed in both terrestrial and simulated altitude environments (Dean, Yip and Hoffman, 1990; Honigman et al., 1993; Maggiorini et al., 1990; Montgomery et al. 1989; Schneider et al., 2002; Shukitt-Hale, 1991; Shukitt-Hale et al., 1990; Shukitt-Hale et al., 1998). Shukitt-Hale, Banderet and Lieberman (1991) find that after 5 to 7 hours at 4,700 m simulated hypobaric hypoxia, changes in AMS correlate most strongly with changes in symptoms, then changes in mood state and finally changes in performance, suggesting differential effects of altitude on these measures. Shukitt and co-workers conclude that the mood state time-course at altitude is similar to the AMS symptoms time-course, specifically AMS cerebral symptoms (Shukitt-Hale 1991). Bardwell, Ensign and Mills (2005) find a similar pattern in their study of the compromised ability to perform critical tasks that accompanies stress-induced negative mood state in 60 male Marine soldiers completing strenuous training at altitudes from 2,053 m to 3,600 m (Bardwell et al., 2005). The increase in mood disturbance from baseline to completion of the training was found to persist in some Marines up to 90 days, with anger and fatigue scores comparable to adult male psychiatric outpatient norms (Bardwell et al., 2005; McNair, 1992).

In a study of mood changes, AMS and cognitive dysfunction Crowley et al. (1992) test 13 male soldiers during a simulated ascent from sea-level to 4,300 m in a hypobaric hypoxic chamber (Crowley et al., 1992). Subjects were exposed to a simulated ascent of 10 minutes to replicate the ascent of an aircraft and remained at 4,300 m for 2.5 days, during which they periodically completed self-report mood scales, AMS assessments and cognitive tests. Crowley and colleagues observe that sick subjects (those who reported an

AMS-cerebral factor score >0.7 on the Environmental Symptoms Questionnaire) displayed more negative mood changes and experienced less improvement in performance over time, which could present a significant safety hazard to military aviators (Crowley et al., 1992). This conclusion about the affects of mood state changes on military performance at altitude support the results and conclusions of Bardwell and colleagues (2005).

Hypoxic Ventilatory Response

One of the most immediate physiological changes observed in humans at high altitudes is an increase in respiration rate that compensates for reduced ambient oxygen. Investigators estimate ventilatory acclimatization to altitude by the hypoxic ventilatory response (HVR), which, when enhanced, increases alveolar O_2 pressure and raises arterial oxygenation (Bisgard and Forster, 1996). In order to more fully understand the mechanisms of respiration in hypoxia the processes must be examined within the context of the body's requirement for oxygen and its acquisition from the surrounding environment.

The primary fuel for cellular reactions in the human body is adenosine triphosphate, or ATP (Freeman, 2005). At the cellular level mitochondria supply the body with ATP by consuming O_2 and metabolizing it to yield ATP and a carbon dioxide (CO_2) byproduct. This process must occur continuously with a carefully regulated homeostasis between O_2 and CO_2 within the body. To transfer oxygen from the environment to the mitochondria the body maintains an oxygen transport cascade that is particularly significant in hypoxic conditions (Sutton et al., 1988). The first step in this

process, ventilation, occurs when CO₂ is expelled from the body and O₂-rich air moves into the lungs and lung alveoli where it diffuses into capillary blood. Diffusion is central to the process of gas exchange in the body as the concentration of O₂ is usually high in the air and low in the tissues, while the concentration of CO₂ is high in tissues and low in the ambient atmosphere (Freeman, 2005; Sutton, 1998; Connett, Honig, Gayeski and Brooks, 1990). As discussed previously, though the percentage of O₂ in the atmosphere remains the same at a high altitude (20.9%), lowered atmospheric pressure results in a lower density of air (Virués-Ortega et al., 2004). There are thus fewer molecules of O₂ and other atmospheric gases per unit volume of air. High altitude researchers express this presence of oxygen in partial pressure, the fractional composition of gas multiplied by the total pressure, notated P_{O_2} . For example, P_{O_2} at sea level is $0.209 \times 760 \text{ mmHg}$, or 160 mmHg, while at the summit of Mt. Everest, with a pressure of approximately 250 mmHg, P_{O_2} drops to 53 mmHg. Oxygen and carbon dioxide diffuse in the alveoli according to the P_{O_2} and P_{CO_2} gradients, flowing from high to low pressures (Connett et al., 1990; Freeman, 2005; Sutton et al., 1988).

The human body must maintain P_{O_2} and P_{CO_2} within a narrow homeostatic range in order to ensure adequate ATP production. At rest the medullary respiratory center at the base of the brain controls these levels through regulation of the respiration rate. During exercise, however, muscle tissue extracts more oxygen from the blood resulting in a drop of P_{O_2} in the blood and an increase in P_{CO_2} as the muscles rapidly metabolize the oxygen (Freeman, 2005). The abundant CO₂ readily reacts with water to form carbonic acid which dissociates into a hydrogen ion and a bicarbonate ion. The excess hydrogen

ions induce a drop in blood pH leading to acidosis. Chemoreceptors near the large arteries in the neck, known as carotid bodies, detect the change in pH and signal the respiratory center in the medulla to increase the respiration rate, thus enhancing the rate of CO₂ expulsion and O₂ intake. The increased excretion of CO₂ also eliminates excess hydrogen ions, stabilizing the pH of the blood and consequently regulating the amount of O₂ that will be transferred from the blood to the tissue (Freeman, 2005; Gallagher and Hackett, 2004; Sutton, 1998).

The ventilatory pathway and the transportation of oxygen in the body is of critical importance to high altitude and laboratory IHE studies. At high altitudes humans compensate for the decrease in ambient P_{O_2} in a progressive, time-dependent increase in ventilation, termed ventilatory acclimatization (Bisgard and Forster, 1996). As stated previously, investigators measure ventilatory acclimatization to altitude by the hypoxic ventilatory response (HVR) which indicates increased sensitivity of the peripheral chemoreceptors to hypoxia (Huang et al., 1984). When enhanced, HVR increases alveolar O₂ pressure and raises arterial oxygenation. Researchers measure HVR by dividing the change in ventilation (ΔV_E) by the oxygen saturation of the blood (Bernardi, Schneider, Pomidori, Paolucci and Cogo, 2006; Levine et al., 1991; Townsend et al., 2002). Even with lowered ambient O₂ levels at mild altitude, if the body is at rest tissue demand for O₂ remains low. With progressively higher altitude or exercise at altitude, the demand for O₂ increases and ventilation must adjust to meet the demand (Bisgard and Forster, 1996). Ventilation increases to limit hypoxemia immediately upon exposure to hypoxia, but this augmentation tempers off slightly in the first hour of exposure in a process known as ventilatory roll-off (Bisgard and Forster, 1996). After the initial peak

increased pulmonary ventilation persists as the body acclimatizes and ventilatory acclimatization continues, primarily mediated by peripheral chemoreceptor sensitivity (Bisgard and Forster, 1996; Dujours, 1962; Rahn and Otis, 1949).

Ventilatory acclimatization thus increases P_{O_2} and decreases P_{CO_2} as oxygen is brought in more quickly than carbon dioxide is produced as a result of hyperventilation (Rahn and Otis, 1949). The condition of lowered carbon dioxide in the blood is referred to as hypocapnia and is indicated by alkalosis, as compared to the acidosis that results from excess carbon dioxide in exercise described previously (Howard and Robbins, 1995). It is possible that the more pronounced increase in ventilation expected from hypoxia-induced acidosis, which would signal carotid body chemoreceptors, is masked at altitude by the associated hypocapnic alkalosis. Howard and Robbins (1995) postulate this interaction in their investigation of the ventilatory response to 8 hours of isocapnic (controlled levels of CO_2) and poikilocapnic (uncontrolled levels of CO_2) hypoxia in humans (Howard and Robbins, 1995). Howard and Robbins observe that in the isocapnic group, where the end-tidal P_{CO_2} ($PEtCO_2$) was held constant, the onset of the ventilatory response was faster than it was in the poikilocapnic group, where $PEtCO_2$ was left uncontrolled. Acclimation to poikilocapnic conditions more closely resembles high altitude acclimatization where there is a progressive increase in ventilation over the course of days or weeks. In these conditions hypocapnic alkalosis develops from the initial hyperventilation that results from the hypoxic stimulation of peripheral chemoreceptors and acts to balance the initial elevation in ventilation (Howard and Robbins, 1995).

Other investigations study the effects of ventilatory acclimatization on the individual's ability to function at high altitudes. Pugh et al. (1963) explore muscular exercise in 6 male subjects at various altitudes from sea-level to 7,440m over the course of 8 months. Maximum consumption of oxygen (VO_{2max}) was found to be inversely related to rise in altitude resulting in a reduced maximal work capacity (Pugh et al., 1963). Dempsey and Forster (1982) find that at 4,300 m HVR increased P_{O_2} approximately 10 mmHg, inspiring a 10% increase in SaO₂ and a 2 volume-percent increase in arterial O₂ content (Ca_{O_2}), which allows for an increase in maximal work output (Dempsey and Forster, 1982).

In an investigation of the individual links in the O₂ transport chain at extreme altitudes, Sutton et al. (1988) examine 8 male subjects at rest and at a steady state of exercise at sea level and at simulated altitudes over the course of 40 days in a simulated ascent of Mount Everest. Sutton and his colleagues observe a fourfold increase in alveolar ventilation and a significant increase in the diffusion of oxygen from capillary blood to tissue mitochondria. They conclude that these mechanisms of acclimatization enable humans to work at ambient pressures and hypoxic conditions previously thought impossible (Sutton et al., 1988). Ceretelli (1976) removes the hypoxic drive in a study of acclimatized subjects on Mt. Everest by applying 100% oxygen and found a failure of subjects to return to sea-level VO_{2max} levels. Ceretelli concludes that reduction in maximal cardiac output is attributable to changes in peripheral circulation, perhaps as a consequence of limited respiratory function of the mitochondria or an impairment of alveolar-capillary O₂ diffusion. The impairment of peripheral circulation may result from hypoxia-induced hematological changes that increase blood viscosity, a problem for

athletes seeking to enhance performance through hematological adaptations to IHE (Cerretelli, 1976).

The mechanisms of altitude physiology and adaptation are of additional interest when applied to athletes and individuals planning to ascend to high altitude. Levine et al. (1991) find that exercise training at altitude results in increased HVR, possibly due to increased chemoreceptor sensitivity, as evidenced in their study of 21 subjects at 2,500m simulated altitude in hypobaric hypoxia for 5 weeks (Levine et al., 1991). Enhanced HVR is viewed as a beneficial adjustment (Huang et al., 1984), especially in highly trained endurance athletes who typically have a blunted HVR (Byrne-Quinn, Weil, Sodal, Filley and Grover, 1971). It is significant to note that Bernardi, Schneider, Pomidori, Paolucci, and Cogo (2006) find that elite climbers who were able to summit Mount Everest without oxygen had a smaller HVR during acclimatization at the base camp at 5,200 m. The researchers suggest that sensitivity to hypoxia may allow more sustainable ventilation in more extreme hypoxia (Bernardi et al., 2006). In an investigation of the effect on HVR of the “living high-training low” (LHTL) model, Townsend et al. (2002) measure HVR in 33 athletes exposed to normobaric IHE simulated altitude for 20 days. Townsend et al. observe that the LHTL model produced an increased HVR in athletes in a time-dependent manner, as well as a decrease in $PEtCO_2$ (Townsend et al., 2002).

In a study of 6 subjects exposed to 4,500m of simulated altitude in a hypobaric hypoxic chamber Ketayama et al. (2001) observe that one week of daily one hour exposure significantly improves tissue oxygenation during exercise in subsequent exposure to acute hypoxia. Adjustments persisted up to one week after final exposure, presumably due to enhanced hypoxic ventilatory chemosensitivity, as evidenced by

increased HVR during exercise (Ketayama, 2001). Savourey et al. (1994) study the physiological effects of preadaptation to high altitude in 7 subjects first acclimatized at 4,350 m, followed by intermittent acclimation in a hypobaric chamber prior to ascent of the Himalayas (7,440 m). Researchers observed increases in PEtCO_2 in hypoxia and higher arterial oxygen saturation of blood and conclude that the pre-acclimatization and intermittent acclimation triggered mechanisms that saved climbers 1-2 weeks of acclimatization during the expedition (Savourey et al., 1994).

Hematological Adaptations

Although less relevant to this study, hypoxia-induced hematological adaptations also help optimize oxygen transport to tissues in hypoxic environments. In establishing a thorough understanding of the physiology of altitude acclimatization or IHE-induced acclimation, especially for prolonged exposure, it is important to note that the ventilatory response does not occur in isolation. Exposure to high altitude longer than one week elicits a posterior adaptive process known as polycythemia, a condition in which there is a net increase in the total number of blood cells in the body (Virués-Ortega et al., 2004). Consider the O_2 transport chain discussed previously. Once oxygen enters the lung alveoli it diffuses along the pressure gradient into the capillary blood. Blood is a connective tissue, 40-50% of which is cells interspersed in a watery extracellular mixture that constitutes the other 50-60% (Freeman, 2005). The red blood cells in this mixture facilitate the transportation of oxygen between the mitochondria and the lungs. As red blood cells develop in stem cell tissue in the bone marrow they lose most typical cell organelles and fill instead with hemoglobin. Hemoglobin consists of four polypeptide chains bound to non-protein groups known as hemes, each with an iron ion that can bind

to an O₂ molecule. Every molecule of hemoglobin can thus bind four molecules of O₂ (Freeman, 2005).

Red blood cells, known alternatively as erythrocytes, are continuously being regenerated via erythropoiesis that is regulated by a glycoprotein produced in the kidneys named erythropoietin (Ratcliffe et al., 1996). Cells in the kidney sense blood oxygen levels and signal the release of erythropoietin when O₂ levels are low, augmenting the rate of erythropoiesis in the bone marrow (Freeman, 2005). The increase in red blood cells has a direct impact on the effective oxygenation of the blood in hypoxic conditions. Researchers investigating the hematological response to altitude thus monitor hematocrit levels, the erythrocyte volume fraction of the blood, to assess the level of altitude-induced polycythemia, as well as erythropoietin levels in the blood (Virués-Ortega et al., 2004). Though polycythemia increases the oxygen carrying capacity of the blood, the increase in red blood cell count also results in heightened blood viscosity (Gallagher and Hackett, 2004), impeding circulation, increasing blood pressure, and inhibiting the ability of the body to respond to sudden increases in metabolic demand for oxygen, such as in exercise (Mirrakhimov and Winslow, 1996). The augmented viscosity may also cause uneven blood flow and decreased cardiac output (West, 1996). In his text book explanation of human physiology at extreme altitude, West (1996) notes that evolutionarily, the erythropoietin control system for erythropoiesis developed at sea-level as a mechanism to replace blood lost in trauma, malnutrition or other maladies, not to respond to altitude-induced tissue hypoxia (West, 1996). Though athletes seek the performance enhancement that may come with polycythemia, they must consider both the benefits and the risks of a response that may possibly be maladaptive.

In an investigation of the determinants of increased erythropoietin release in hypobaric hypoxia Ge et al. (2001) measure blood erythropoietin levels, oxygen saturation of blood and oxygen content of urine in 48 subjects exposed to four different altitudes for 24 hours per week for 4 weeks at treatment altitudes of 1,780 m, 2,085 m, 2,454 m, and 2,800 m (Ge et al., 2001). Ge et al. observe a significant increase in erythropoietin levels after 6 hours at all altitudes and a continued increase at the higher altitudes, concluding that an altitude-induced increase in erythropoietin release is dependent on dose and degree of hypoxic exposure specifically greater than or equal to altitudes of 2,100 – 2,500 m. Ge and his co-workers also site an erythropoietin release at lower altitudes mediated by a short-term acclimation process and emphasize the significant level of individual variability (Ge et al., 2001). Chapman, Stray-Gundersen and Levine (1998) explore individual variability relative to the magnitude of increase of erythropoietin concentration in responders versus non-responders in a “live high-train low” 28 day training study of 39 collegiate runners. The researchers observe that responders displayed a significantly higher increase in erythropoietin concentration which leads to an increase in total red cell volume and the maximum consumption of oxygen (Chapman et al., 1998). Heinicke et al. (2002) study the erythropoietin response in Chilean soldiers exposed to long term intermittent hypoxia, short term intermittent hypoxia or chronic hypoxia in residents at an altitude of 3,550 m. The researchers find that the total hemoglobin mass and red blood cell volume in the acclimatization to long-term IHE (in this case 22 years) resembles the adaptation to chronic hypoxia seen in permanent residents of high altitude, including increased erythropoietin volume in plasma (Heinicke et al., 2002).

While Heinicke et al. investigate the effects of long-term IHE on erythropoietin and hematological indicators, Richardson, Lodin, Reimers and Schagatay (2007) find that short-term hypoxia (20 minutes) is sufficient to initiate a spleen contraction and subsequent release of stored erythrocytes (Richardson et al., 2007). In this study the researchers observed five subjects exposed to 20 minutes of hypoxic breathing induced via mask (12.8% oxygen, equivalent to 4,100 m simulated altitude) and recorded spleen volume, hemoglobin concentration and hematocrit levels before, during, and after the exposure. The researchers find a 34% reduction in oxygen saturation of blood, an 18% reduction in spleen volume and a 2.1% increase in hemoglobin and hematocrit, as well as an increased heart rate during hypoxia. SaO₂ returned to standard sea level values within 3 minutes after exposure and within 10 minutes spleen volume, hemoglobin and hematocrit all returned to pre-exposure levels. The researchers conclude that hypoxia plays an important role in triggering spleen contraction to induce a release of stored erythrocytes, perhaps as an early adaptive mechanism in humans (Richardson et al., 2007). There is thus consensus that hypoxia-induced hematological alterations are not simply a result of an increase in erythropoietin and subsequent erythropoiesis. Magnitude of elevation and degree of hypoxia as well as the duration of exposure are extremely relevant in determining the extent of physiological adaptation, further complicated by the significant variance in individual responses. From these respective studies it is evident that hematological mechanisms of acclimation to hypoxia are multidimensional. This kind of research has important implications for competitive endurance athletes seeking to extend their aerobic threshold during athletic performance through enhanced tissue oxygenation achieved through simulated altitude and

hematological acclimation (Heinicke et al., 2002; Levine et al., 1991; Levine, 2002; Levine 2005; McClean, 2005; Rodríguez et al., 1999; Townsend et al., 2002).

Normobaric and Hypobaric Hypoxia

While there is great potential for both AMS attenuation and performance-enhancement through simulated altitude, research has revealed that accurately simulating altitude to activate the necessary physiological mechanisms is difficult (Savoirey et al., 2003). The two standard methods of simulating high altitude in the laboratory setting both involve lowering partial pressure of ambient oxygen to induce hypoxemia. In normobaric hypoxia the desired conditions are achieved by lowering the O₂ fraction in the ambient air, while hypobaric hypoxia involves a reduction in barometric pressure (Savoirey et al., 2003). Though these two methods both yield hypoxemia in humans the question of whether there are physiological differences between hypobaric hypoxia and normobaric hypoxia is still unanswered. There are few published studies on this topic and the studies that have been published are inconclusive (Savoirey et al., 2003).

Savoirey, Launay, Besnard, Guinet and Travers (2003) explore the possible physiological differences between hypobaric and normobaric hypoxic systems in 18 subjects exposed for 40 minutes to ambient O₂ partial pressures equivalent to 4,500 m. The researchers observe that compared to the normobaric hypoxic exposure, hypobaric exposure leads to greater hypoxemia, hypocapnia (decreased arterial carbon dioxide), blood alkalosis and a lower oxygen saturation of the blood. Savoirey et al. propose that these results may be a result of an increase in dead space ventilation, which refers to the respiratory gas that does not participate in the gas exchange in the lungs, possibly as a result of the decreased barometric pressure (Savoirey et al., 2003).

Roach, Loeppky and Milton (1996) find a similar pattern, observing that acute mountain sickness was greater and appeared earlier in hypobaric hypoxia as opposed to normobaric hypoxia at equivalent ambient O₂ partial pressures, though the researchers did observe some AMS in normobaric conditions (Roach et al., 1996). Even so, research indicates that extended intermittent exposure to normobaric hypoxia in athletes can induce physiological changes similar to what is observed at high altitudes (Levine, 2002; Townsend et al., 2002). Knaupp, Khilnani, Sherwood, Scharf and Steinberg (1992) find that intermittent exposure to normobaric hypoxia (10.5% oxygen) lasting 6 hours may induce an increase in erythropoietin production (Knaupp et al., 1992). Researchers conducting further investigations observe that 8 hours of hypoxia using an oxygen fraction of 12.9% oxygen for 8 hours per day for 3 days significantly increases erythropoietin (240%) but is not sufficient to propagate the erythropoietic cascade (McClellan, 2005). Rodríguez et al. (1999), however, find that 9 days of 3 to 6 hours of hypobaric hypoxia equivalent to 4,000 – 5,000 m improved aerobic performance capacity in 17 mountaineers (Rodríguez et al., 1999). These results suggest a significant difference in the physiological responses produced through exposure to hypobaric hypoxia and those produced by normobaric hypoxia. Normobaric hypoxia is, however, a considerably simpler method for simulating the conditions of high altitude. Developing a clearer understanding of the specific response to the two methods of altitude simulation is thus an important area for further research.

Methods

Subjects

Fifteen healthy, fully informed voluntary male (n=7) and female subjects (n=8) (all data presented as mean \pm SEM; age: 19.93 \pm 1.35 yr; height: 172.3 \pm 9.8 cm; weight: 70.1 \pm 17.0 kg) participated in this study which was approved by the College of William and Mary Protection of Human Subjects Committee. All of the subjects were nonsmokers, none were born at an altitude greater than 1,500 m, none had traveled to altitudes greater than 1,500 m during the preceding 6 months and all were screened by health history questionnaires (Appendix A) for evidence of anemia of hemoglobin S-type or any other conditions that would make participation more hazardous. All health history forms were reviewed by the project medical director or his designate. If approved for the study, each subject gave written, informed consent (Appendix B) prior to a familiarization session in which they practiced all testing procedures and became comfortable with the sights and sounds of the normobaric hypoxia chamber.

Research Location

The Jack Borgenicht Altitude Physiology Research Facility (JBAPRF) is located in Adair Hall, Room 108 on the campus of The College of William and Mary in Williamsburg, Virginia. The laboratory is located at an altitude of approximately 15 m with a standard barometric pressure of 752 mmHg depending upon weather conditions. The facility consists of a normobaric hypoxic chamber (Colorado Altitude Training Systems, Boulder, CO) within which the partial pressure of oxygen can be finely controlled to simulate atmospheres found at altitudes from sea-level to 18,000 feet.



***The Jack
Borgenicht
Altitude
Physiology
Research Facility***

***The College of
William and Marv***



Air Units – each capable of extracting specific amounts of oxygen from up to 10L of ambient air per minute.

The normobaric hypoxia chamber operates at a “normal” sea level atmospheric pressure of approximately 760 torr (1 torr = 1/760 atmosphere), typical sea level barometric pressure. The air units associated with this chamber can extract oxygen from external air that is then pumped into the chamber and maintain a preset simulated altitude while subjects are inside.

As discussed, the fraction of O₂ in the atmosphere remains the same at 20.9% regardless of the altitude. At sea-level the atmospheric pressure is 760 mmHg, which means 159 mmHg O₂ is the part of the total atmospheric pressure produced by its fraction of oxygen. The balance is made up of nitrogen, inert gases, and a very small amount of carbon dioxide. At 4,300 meters (14,100 ft.) the barometric pressure is 462 mmHg and the fraction of the atmosphere made up of oxygen is still 20.9% producing a (partial) pressure of 96 mmHg. This reduced partial pressure of oxygen pushes oxygen into the bloodstream across a lower gradient resulting in less oxygen carried by the blood to body tissues. This lower oxygen (hypoxia) can result in Acute Mountain Sickness (AMS) and in extreme cases, much more serious illnesses such as High Altitude Pulmonary Edema (HAPE) or High Altitude Cerebral Edema (HACE). It is also interesting that many diseases, both chronic and acute, result in decreased oxygen supply to body tissues (hypoxia). Research that examines the body’s physiological response to hypoxia may be helpful in numerous ways.

Within very narrow limits, the Colorado Altitude Training System (Boulder, CO), allows simulation of various altitudes from sea level to 18,000 feet. By operating the system without filtering out oxygen, the sounds and feel of the chamber are exactly the same at sea level as they are at high altitude. This is imperative when conducting control

experiments. Room air is pumped through the 4 air units at a rate of 10L/minute. This air, with its lowered oxygen fraction, is then recycled through the chamber by 3 of the air units while unit 4 introduces fresh room air that has also had its oxygen reduced. This accomplishes two objectives. First, desired altitude is maintained within narrow limits and second, it is achieved without having to reduce the barometric pressure, which would require a very expensive steel chamber in which vacuum pumps reduce the ambient pressure to create “hypobaric” hypoxia.

Protocol

After approval and voluntary informed consent, each subject was first familiarized with all testing procedures in the Jack Borgenicht Altitude Physiology Research Facility. During the familiarization session subjects completed practice questionnaires, and measurements were made of height (standard fixed stadiometer), weight (Taylor Precision Products, Las Cruces, NM), blood pressure (Omron HEM-78ON3, Bannockburn,, Ill), resting heart rate (HR) (BP Monitor or SaO₂ Monitors), oxygen saturation of blood ([SaO₂], Nonin ONYX 9500 or IPX3 pulse oximeter, Plymouth, MN), and resting end-tidal CO₂ ([PEtCO₂], Nellcor NPB-75, Pleasanton, CA). Subjects were then divided into two groups; 1) Control Group (n=4), and 2) IHE Group (n=11). All IHE (treatment) subjects were exposed to a normobaric simulated altitude of 4,300 m for 3 hours on 3 consecutive days, after which they returned to the altitude lab exactly 24 hours after the last 3h exposure were they at a simulated altitude of 4,300 m for approximately 1 hour (IHE +24h; n=6). Five of the IHE group returned to the laboratory 48 hours after their last 3h exposure for a 1 hour stay at 4,300 m simulated altitude (IHE +48h; n=5). Controls (n=4) followed the same protocol except that

chamber air was not filtered of any oxygen as it passed through the air units thus always maintaining sea level partial pressure of oxygen in the chamber atmosphere. Before and after exposure to sea level or simulated 4,300 m altitude, all subjects were administered four tests: the Profile of Mood State (POMS; MHS, North Tonawanda, NY, Appendix C), the Environmental Symptoms Questionnaire III (ESQ-III; Sampson, Cymerman, Burse, Maher and Rock. 1983, Appendix D), the Lake Louise Consensus Score Questions (LLSQ; Roach, Bärtsch, Oelz, and Hackett, 1993, Appendix E) and a 14- minute resting ventilation test during which $PEtCO_2$, respiratory rate ([RR], Nellcor NPB-75, Pleasanton, CA.), and SaO_2 were recorded. Weight was measured before and after each exposure to ensure adequate hydration. After resting ventilation tests, all subjects entered the chamber and immediately completed the Feelings Profile (FP; Jackson and Kambis, 1991, Appendix F). Subjects could then study, watch DVDs, or read for the remainder of the exposure. Subjects were prohibited from sleeping or exercising during any phase of the study. For the duration of the exposure heart rate and oxygen saturation of arterial blood were recorded every fifteen minutes, after which each subject would complete the Feeling Profile.

Incidence and severity of AMS were assessed using the LLSQ and the ESQ-III questionnaires. The Lake Louise consensus questions about AMS symptoms and signs are generally divided into a self-report section and a clinical section. For the purposes of this study the LLSQ was limited to just the self-report section. This section consists of five multiple choice questions that ask the subject to rate the severity of headache, gastrointestinal symptoms like nausea or vomiting, fatigue and weakness, dizziness and the quality of sleep. Each question and answer has an assigned point score. The sum of

the points of these questions yields the AMS self-reported score. The ESQ-III contains a list of 68 symptoms and allows researchers to assess various environmental stresses, in this case simulated high altitude. For the purposes of this study, only the AMS-cerebral (AMS-C) score was examined, which encompasses similar symptoms as the LLSQ (i.e. dizziness, nausea, weakness etc.) (Sampson et al., 1983). The letter C designates “cerebral”, as these symptoms appear to be correlated with altered cerebral function.

Mood disturbance was assessed via the POMS and the FP. The POMS mood scale is a paper and pencil 65 item questionnaire that was administered both before and after each exposure in the normobaric chamber. A shortened version, the Feelings Profile, is a 19-item questionnaire administered via touch-screen (Jackson and Kambis, 1991). Both questionnaires yield a calculation of Total Mood Disturbance (TMD), which is the score used in this study to assess the impact of normobaric simulated altitude on mood state (Kambis, Barnes, Chamberlain, Artese, Tsui and Stanley, 2006; Kambis et al. 2003; Kambis, et al. 2002; McNair et al., 1992).

Both the physiological responses indicators and the self-reported mood state parameters were analyzed by independent t-tests or pair t-tests. Statistical significance was set at $P < 0.05$ for all statistical tests.

Results

PEtCO₂

Exposure to normobaric hypoxia induced a ventilatory response in all subjects at a simulated altitude of 4,300 m (n=11). Both the IHE +24h group and the IHE +48h group displayed a similar pattern of response for days 1, 2, and 3 (see figure 1) and further analysis revealed no significant ($p>0.05$) difference between mean percent change of pre- and post-exposure for the two groups (see figure 2 and table 1). The results for day 1, day 2 and day 3 were thus combined to provide a comparison for the results of the +24h exposure and the +48h exposure (figure 3). This method of comparison was used in all subsequent analyses.

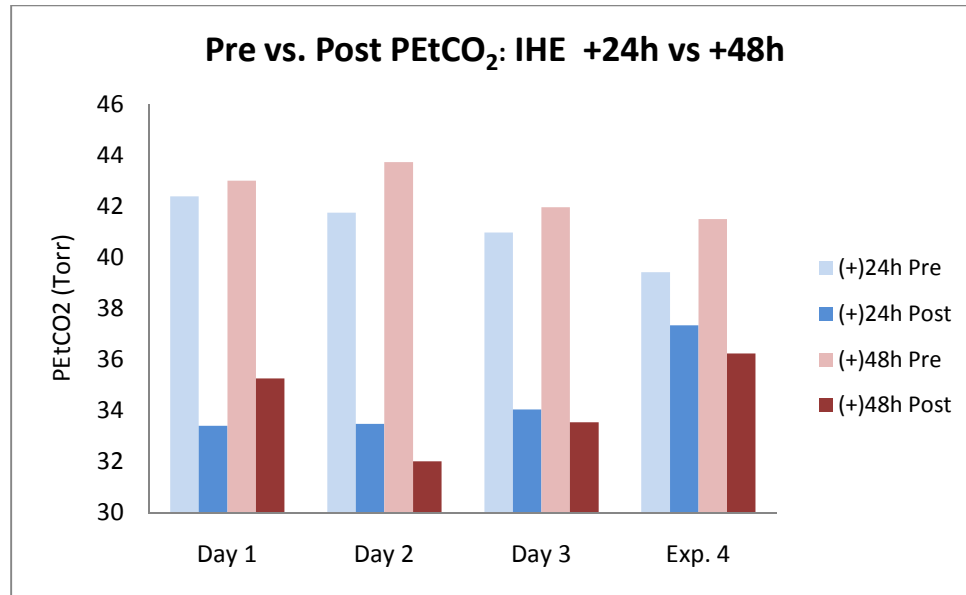


Figure 1: Pre vs. Post PEtCO₂: IHE +24h vs. +48h. Reduction in PEtCO₂ from pre-exposure to post-exposure displayed a similar pattern in IHE subjects for day 1, day 2, day 3 and day 4.

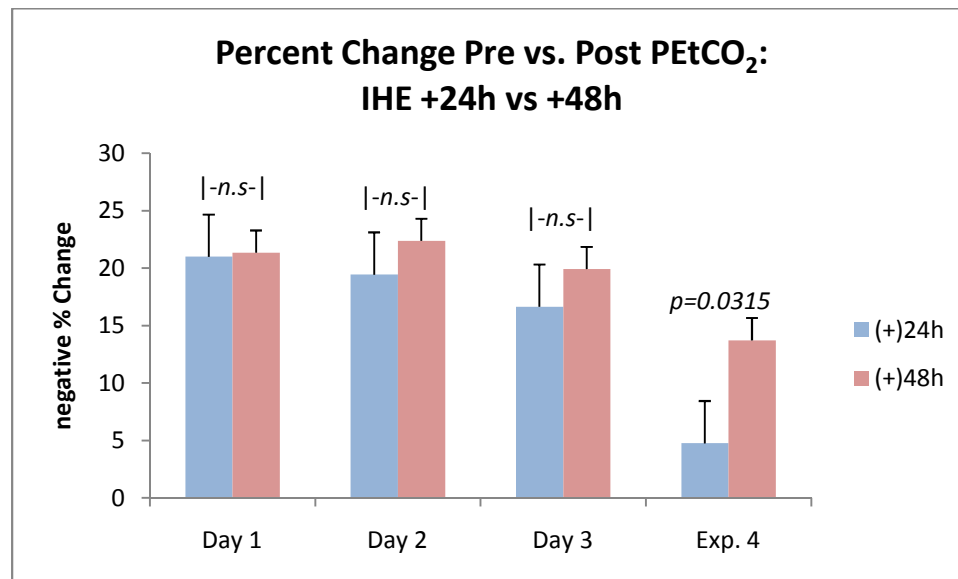


Figure 2: Percent Change Pre vs. Post PEtCO₂: IHE groups +24h vs +48h. No significant ($p > 0.05$) difference was found in pre- and post-exposure percent change between IHE +24h ($n=6$) and IHE +48h ($n=5$) for days 1, 2 and 3. A significant ($p < 0.05$) was observed between exposure 4 percent change between the two IHE groups.

<u>Day</u>	<u>%change</u> +24h (n=6)	<u>%change</u> +48h (n=5)	<u>p-value</u>
Day 1	21.0	21.4 [†]	0.1196
Day 2	19.5	22.4	0.4126
Day 3	16.7	19.9	0.1313
Exp 4	4.76	13.7 ^{††}	0.0315*

[†]One post-exposure reading for an IHE +48h subject was discarded due to mechanical malfunction of the capnograph. Percent change for this day was calculated from n=4.

^{††}Two post-exposure readings for IHE +48h subjects were discarded due to mechanical malfunction of the capnograph. Percent change for this day was calculated from n=3.

The mean values of PEtCO₂ showed a significant ($p < 0.001$) decrease from pre-exposure to post-exposure for days 1, 2 and 3 in all IHE subjects (figure 3). The mean pre- and post- PEtCO₂ values are summarized in table 2. Periodic malfunctioning of the capnograph resulted in erroneous data for one IHE +48h subject for post- day 1 and day 2, and two other IHE +48h subjects for post- exposure 4 PEtCO₂ readings. This data was discarded and mean PEtCO₂ values were calculated with these subjects removed from the sample.

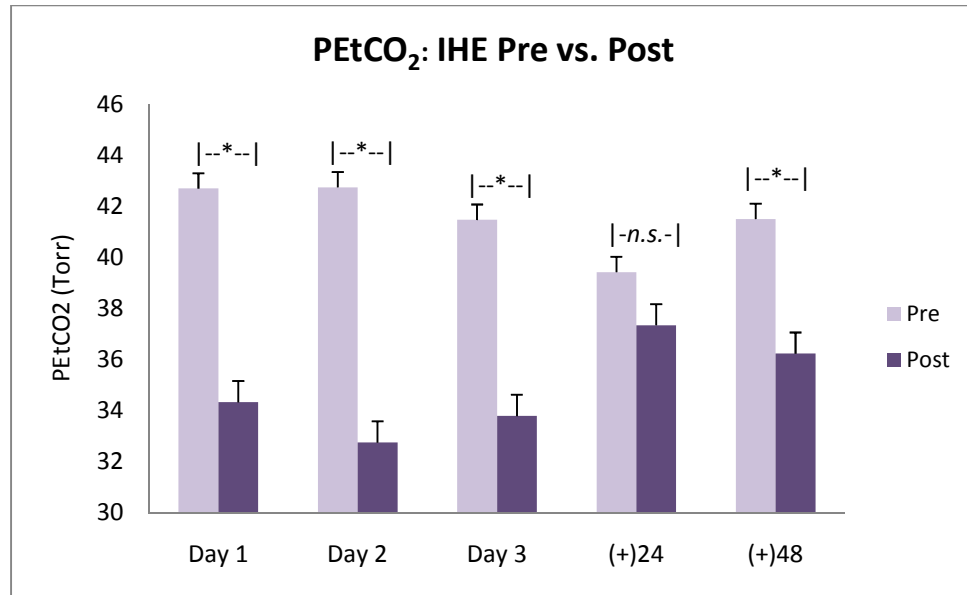


Figure 3: Pre vs. Post PEtCO₂: IHE. The reduction in PEtCO₂ was significant ($p < 0.001$) for all IHE subjects ($n = 11$) for day 1, day 2, and day 3. There was no difference ($p > 0.05$) between pre- and post-exposure PEtCO₂ in the fourth exposure of the IHE +24h group. There was, however, a significant ($p < 0.05$) reduction from pre- to post-exposure in the fourth exposure of the IHE +48h group.

<u>Day</u>	<u>Pre (Torr)</u>	<u>Post (Torr)</u>	<u>p-value</u>
Day 1 (n=10) [†]	42.7	34.3	0.000*
Day 2 (n=11)	42.7	32.7	0.000*
Day 3 (n=11)	41.5	33.8	0.000*
+24 (n=6)	39.4	37.3	0.109
+48 (n=3) ^{††}	41.5	36.2	0.013*

[†]One IHE +48h post PEtCO₂ value was discarded due to mechanical error.

^{††}Two IHE +48h post PEtCO₂ values were discarded due to mechanical error.

Further analysis of pre- vs. post percent change between exposure days indicated a significance ($p < 0.001$) between day 1 and IHE +24h, as well as a significance ($p < 0.01$) between day 1 and IHE +48h (figure 4). As shown in table three and figure 4, there was a significant ($p < 0.05$) difference between exposure 4 of IHE +24h and IHE +48h and a significant ($p < 0.001$) difference between day 3 and the +24h group. There was not, however, a difference between day 1 and day 3 or between day 3 and the +48h group ($p > 0.05$).

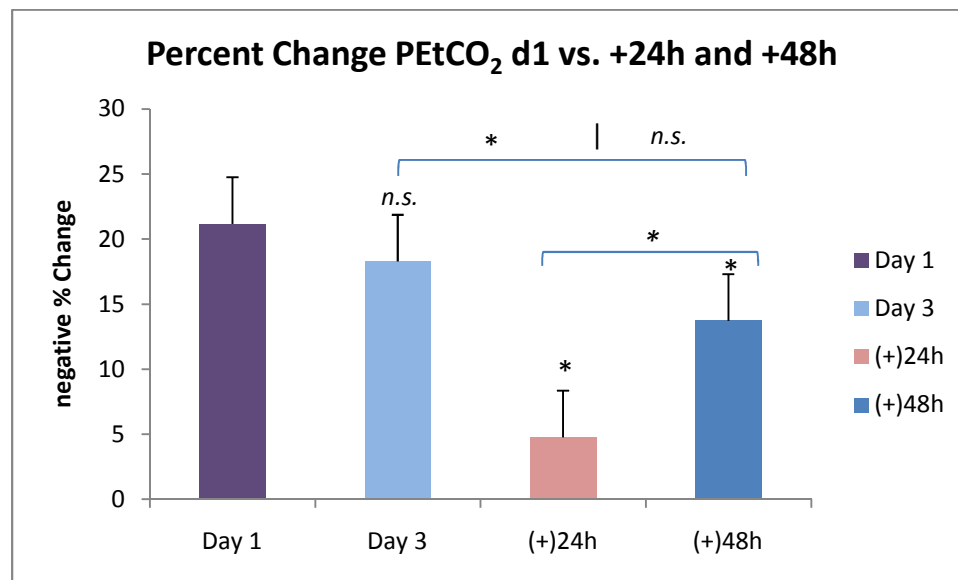


Figure 4: Inter-day comparisons of percent change in IHE PETCO₂. The difference in percent change was significant between day 1 and +24h ($p < 0.001$), day 1 and +48h ($p < 0.05$), +24h and +48h ($p < 0.05$) and day 3 and +24h ($p < 0.001$). There was no difference between day 1 and day 3 ($p > 0.05$), or between day 3 and +48h ($p > 0.05$).

<u>Comparison</u> a vs. b	<u>Percent Change</u>		<u>P value</u>
	a	b	
Day 1 [†] vs. Day 3	21.2%	18.1%	0.188
Day 1 [†] vs. +24h	21.2%	4.76%	0.000*
Day 1 [†] vs. +48h	21.2%	13.7%	0.008*
+24h vs. +48h	4.76%	13.7%	0.032*
Day 3 vs. +24h	18.1%	4.76%	0.000*
Day 3 vs. +48h ^{††}	18.1%	13.7%	0.069

†One IHE +48h post PEtCO₂ value was discarded due to mechanical error.

††Two IHE +48h post PEtCO₂ values were discarded due to mechanical error.

Heart Rate and SaO₂

Figure 5, figure 6 and figure 7 show mean heart rate and oxygen saturation of blood for all four days for the control group and both the IHE +24h and the IHE +48h groups. To standardize comparisons between the first three days and the fourth exposure, mean values were calculated from the first 45 minutes of each exposure. No difference was found between day 1 and the exposure 4 for any of the groups (figure 8, figure 9, figure 10 and table 5).

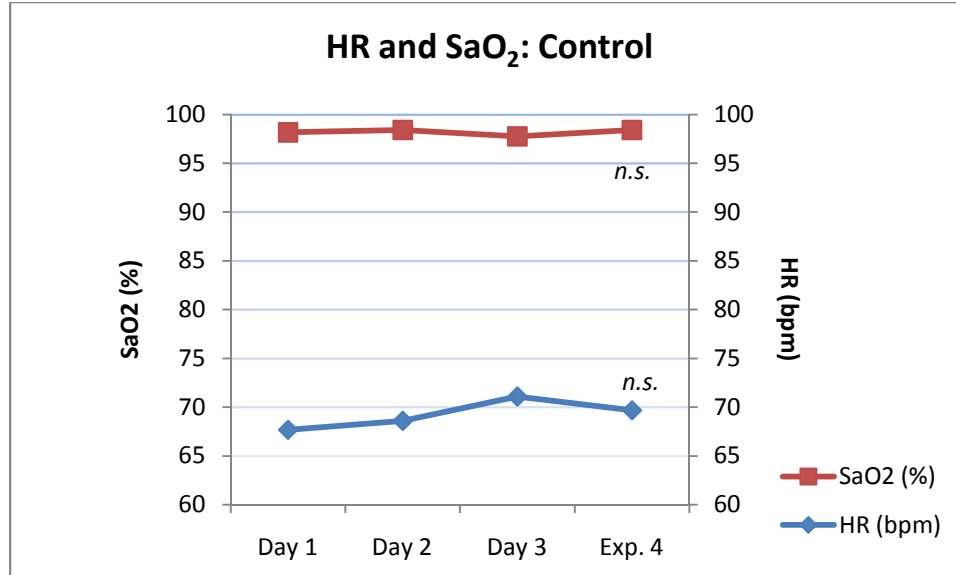


Figure 5: HR and SaO₂: Control. Mean heart rate and oxygen saturation of blood for control group (n=4). No difference was observed between day 1 and exposure 4 for either hr or SaO₂ ($p>0.05$). See table 5.

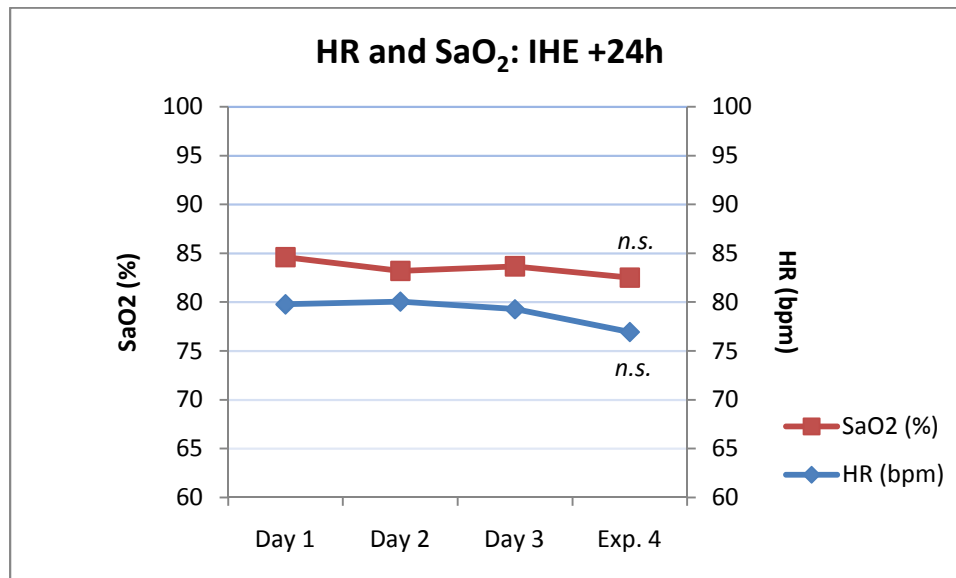


Figure 6: HR and SaO₂: IHE +24h. Mean heart rate and oxygen saturation of blood for IHE +24h group (n=6). No difference was found between day one and exposure 4 for either HR or SaO₂ ($p>0.05$). See table 5.

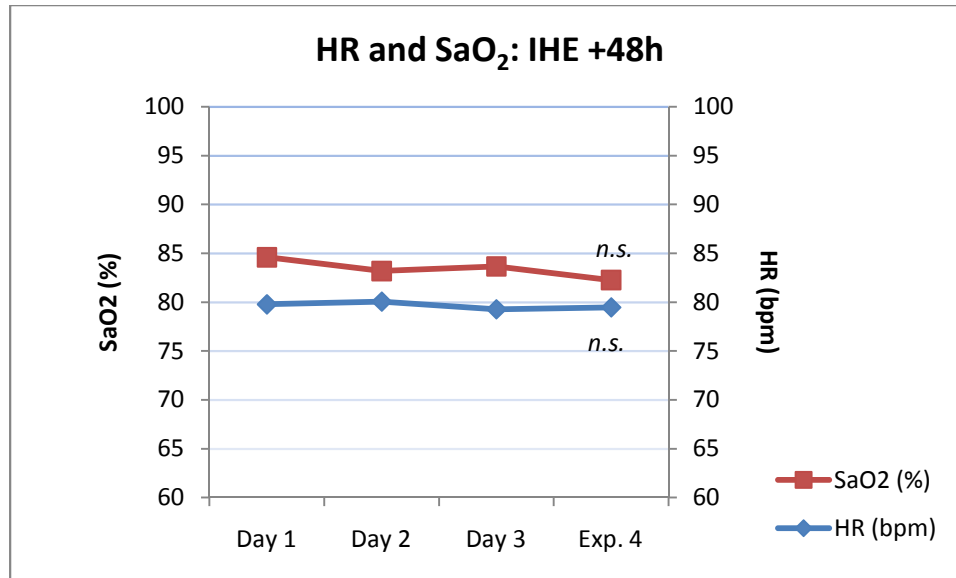


Figure 7: HR and SaO₂: IHE +48h. Mean heart rate and oxygen saturation of blood for IHE +48h group (n=5). No difference was found between day one and exposure 4 for either HR or SaO₂ ($p>0.05$). See table 5.

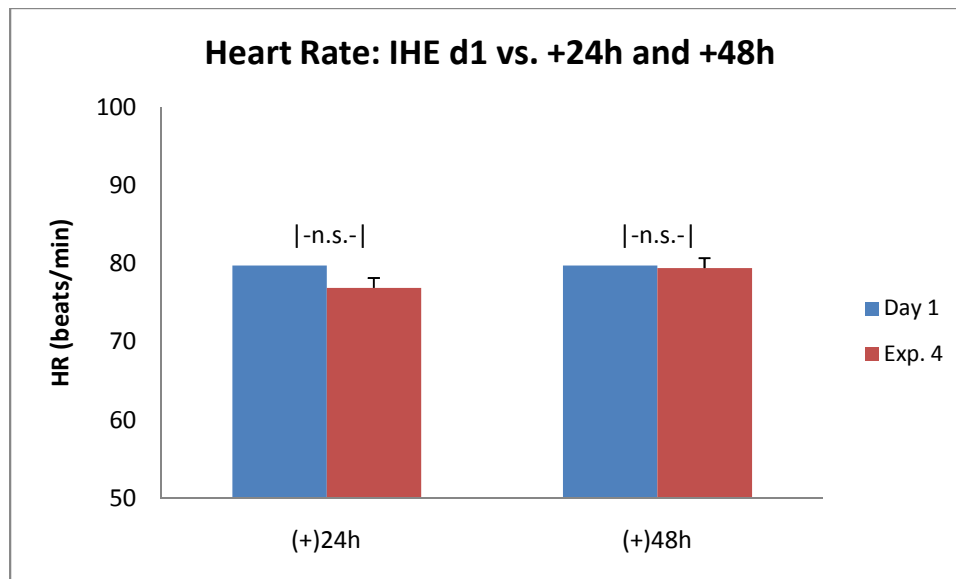


Figure 8: IHE HR d1 vs IHE +24h and +48h. No difference was observed between mean HR day 1 and exposure 4 of the +24h (n=6) and +48h (n=5) groups ($p>0.05$). See table 4.

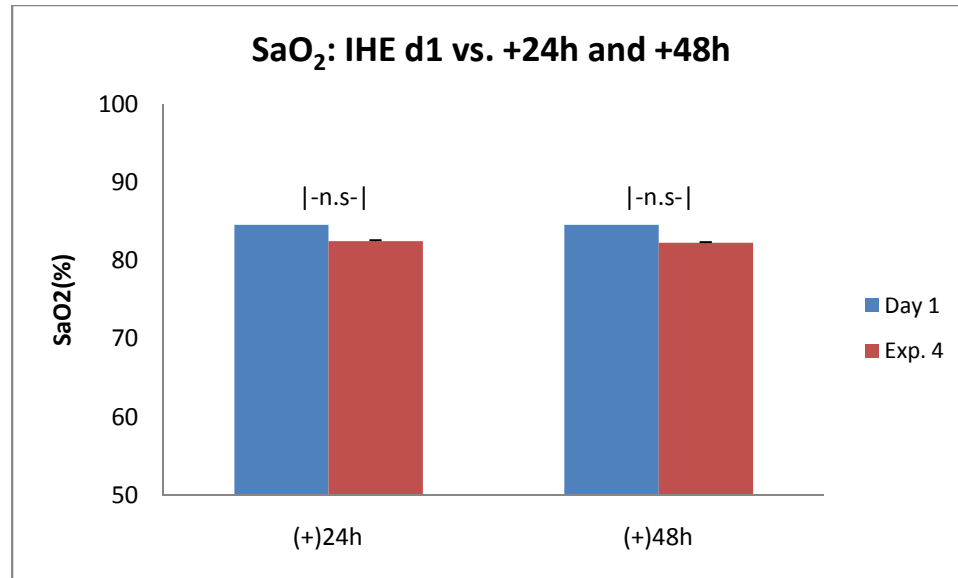


Figure 9: IHE SaO₂ d1 vs. IHE +24h and +48h. No difference was observed between mean SaO₂ day 1 and exposure 4 of the +24h (n=6) and +48h (n=5) groups (p>0.05). See table 4.

As shown in figure 8 and figure 9, there was no difference observed between day 1 and the fourth exposure for either IHE group. The comparisons of mean values are summarized in table 4.

	Day 1 (n=11)	+24h (n=6)		+48h (n=5)	
	mean	mean	<i>p-value</i>	mean	<i>p-value</i>
HR (bpm)	79.6	76.9	0.298	79.5	0.495
SaO ₂ (%)	84.7	82.5	0.145	82.3	0.466

No difference observed between day 1 and exposure 4 HR and SaO₂ for both IHE groups (p>0.05).

No significance was observed between day 1 and exposure 4 in the control group for both HR and SaO₂, as shown in figure 10 and summarized in table 5.

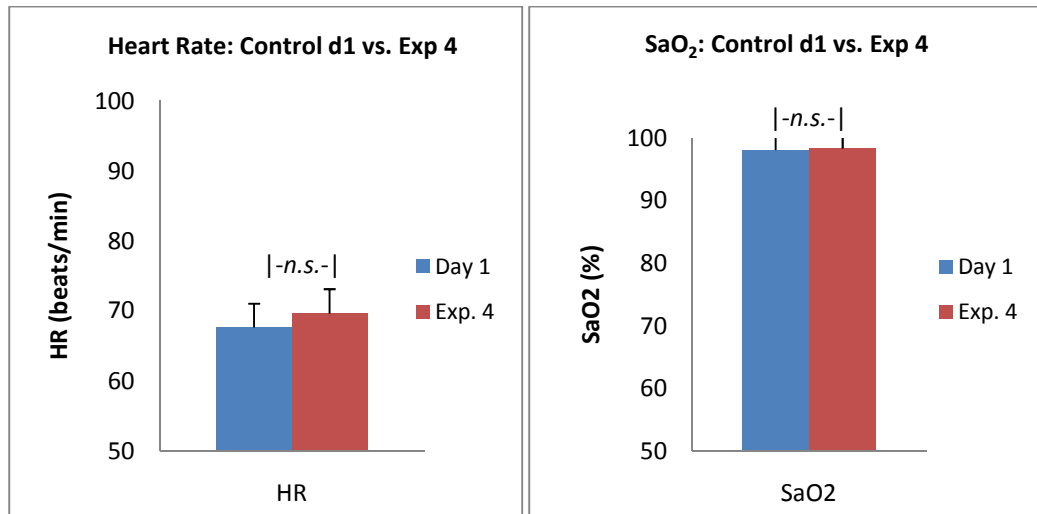


Figure 10: Control HR and SaO₂ d1 vs. control exposure 4. No difference was observed between mean HR or SaO₂ day 1 and exposure 4 of the control group (n=4, p>0.05).

	<u>Day 1</u> mean (n=4)	<u>Day 4</u> mean (n=)		<i>p-value</i>
HR (bpm)	67.7	69.7		0.193
SaO ₂ (%)	98.2	98.4		0.347

No significance found between day 1 and exposure 4 HR and SaO₂ observed in the Control group (p>0.05).

There were, however, several differences found in HR and SaO₂ in a comparison of Control and IHE groups (table 6). The mean HR of the Control group was significantly lower than the mean HR of the IHE group for day 1 and day 2 (p<0.05), but there was no difference between control exposure 4 and IHE +24h exposure 4 (p>0.05). When control exposure 4 was compared to IHE +48, however, the mean control HR was again significantly lower than the IHE group (p<0.01) (figure 11). The mean values for

SaO₂ were significantly lower for both IHE groups when compared to the control group for all exposures ($p < 0.001$) (figure 12).

Table 6: HR and SaO₂: Control vs. IHE						
<u>Day</u>	<u>Heart Rate (bpm)</u>			<u>SaO₂ (%)</u>		
	<u>Control</u> (n=4)	<u>IHE</u> (n=11)	<u>p-value</u>	<u>Control</u>	<u>IHE</u>	<u>p-value</u>
Day 1	67.7±3.21	79.6±9.41	0.015*	98.2±0.333	84.7±3.99	0.000*
Day 2	68.6±6.75	80.0±7.91	0.012*	98.4±0.167	83.3±3.85	0.000*
Day 3	71.0±2.22	79.3±10.1	0.069	97.8±1.23	83.76±2.13	0.000*
Exp. 4 (+24h) (IHE n=6)	69.7±2.83	76.9±9.84	0.097	98.42±1.17	82.5±4.04	0.000*
Exp. 4 (+48h) (IHE n=5)	69.7±2.83	79.5±4.79	0.004*	98.42±1.17	82.3±4.66	0.000*

Significance observed between Control and IHE groups in mean HR for day 1 and day 2 ($p < 0.05$), and between Control exposure 4 and IHE +48h ($p < 0.01$). No significance was found between Control and IHE +24h HR on day 3. Strong significance was found between Control and IHE groups for SaO₂ all days ($p < 0.001$).

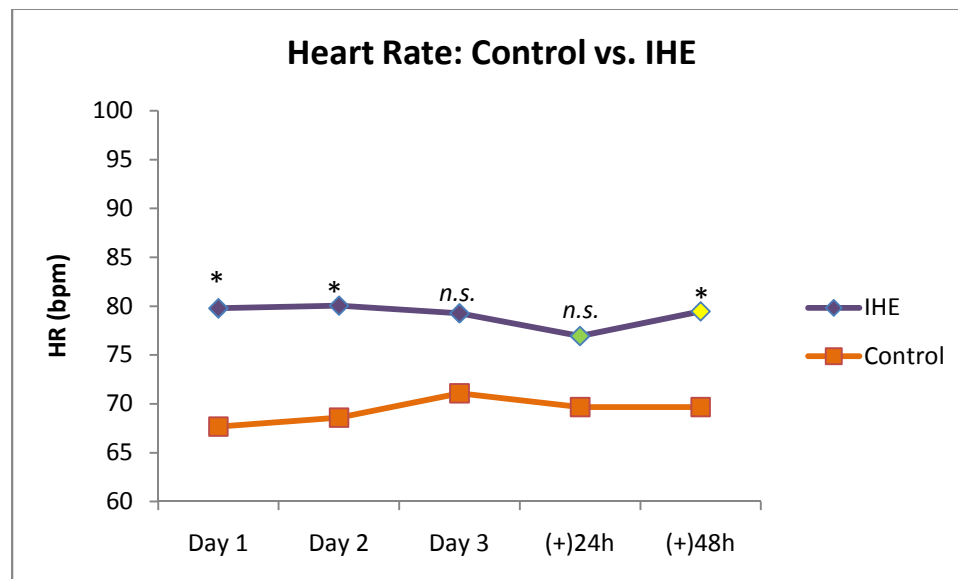


Figure 11: Heart Rate in Control vs. IHE. IHE heart rate was significantly higher than Control means for day 1 and day 2 ($p < 0.05$). No difference was found in heart rate between the two groups for day 3 or for the control exposure 4 and IHE +24h. There was, however, a difference between the control exposure 4 and IHE +48h ($p < 0.05$).

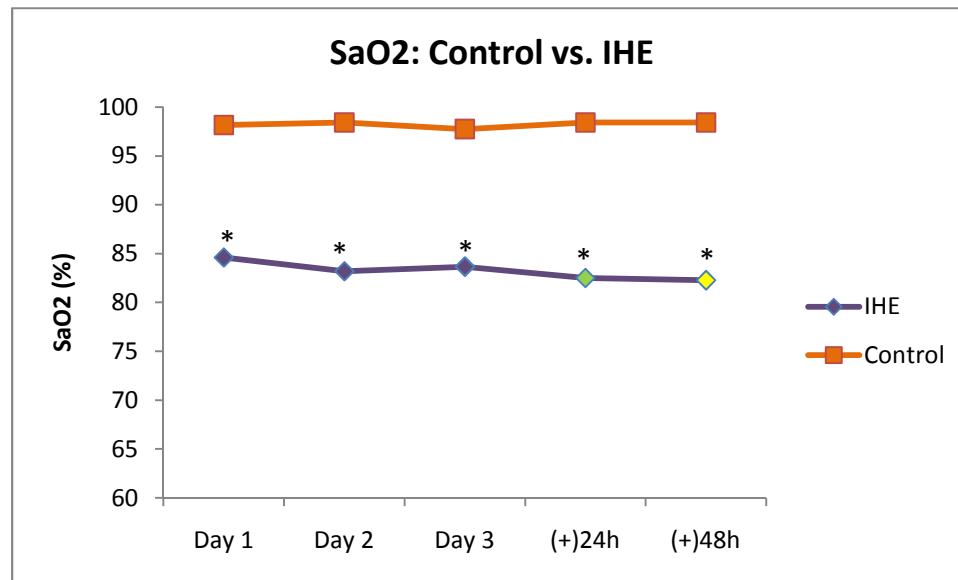


Figure 12: SaO₂ in Control vs. IHE. IHE oxygen saturation of blood was significantly lower than Control means for all days ($p < 0.001$).

Acute Mountain Sickness

Environmental Symptoms Questionnaire-III: Acute Mountain Sickness-cerebral score

Acute mountain sickness was assessed using the AMS-cerebral (AMS-C) score of the ESQ-III self report questionnaire. Significance between pre- and post-exposure AMS-C scores was observed only on day 1 for both the Control and the IHE groups, and not on any other day (figure 13, figure 14 and table 7).

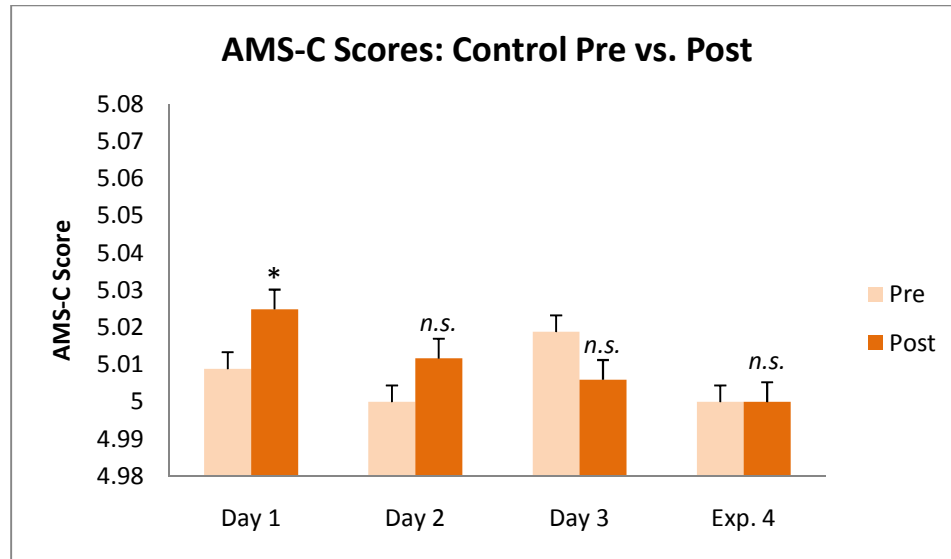


Figure 13: Pre vs. Post AMS-C Scores: Control. A difference was observed between pre- and post-exposure AMS-C scores in the control group (n=3) only on day 1 ($p < 0.01$). No significance was found for day 2, day 3 or exposure 4 ($p > 0.05$). Due to self-reported unusual and extreme stress from outside factors, the ESQ-III data for one control subject was discarded. Mean values and significance scores were calculated from the remaining control group (n=3).

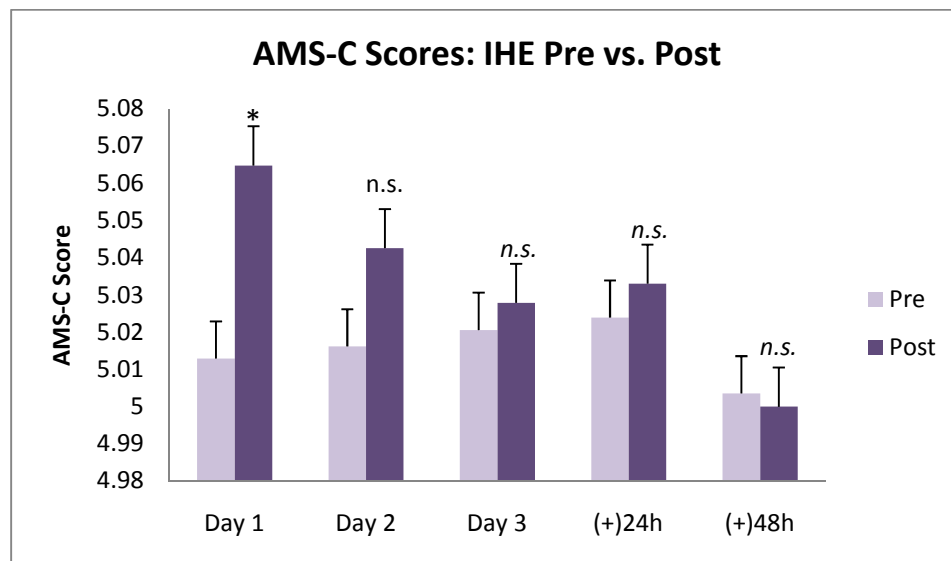


Figure 14: Pre vs. Post AMS-C Scores: IHE. A significant increase was observed from pre- and post-exposure AMS-C scores in the IHE group (n=11) on day 1 ($p < 0.05$), but not on day 2, day 3 or for IHE +24h (n=6) ($p > 0.05$). There was a slight decrease in the AMS-C score for the fourth exposure in the IHE +48h (n=5) group, but it was not significant ($p > 0.05$).

Table 7: AMS-C pre vs. post all subjects (n=14)			
	<u>Control</u>	<u>IHE</u>	
	Total (n=3)	+24 (n=6)	+48 (n=5)
Day 1: pre	5.03±0.05	5.01±0.02	
post	5.11±0.01	5.07±0.09	
<i>p-value</i>	0.004*	0.0265*	
Day 2: pre	5.00	5.02±0.03	
post	5.00	5.04±0.04	
<i>p-value</i>	no variance	0.0656	
Day 3: pre	5.00	5.02±0.03	
post	5.03±0.03	5.03±0.04	
<i>p-value</i>	0.091	0.301	
Exp 4: pre	5.00	5.02±0.04	5.00
post	5.00	5.03±0.04	5.00
<i>p-value</i>	no variance	0.355	no variance

A difference was observed only between pre and post exposures on day 1 of both the control and the IHE group ($p < 0.01$ and $p < 0.05$, respectively). No changes were otherwise significant.

In addition, an analysis of the post-exposure AMS-C scores revealed no significant change from day 1 values to the post-exposure values of any other day for both the IHE and the Control group, with the exception of the IHE +48h fourth exposure ($p < 0.01$) (figure 15 and figure 16). In addition, as shown in table 8, there was significance observed between the +24h exposure and the +48h exposure ($p < 0.05$).

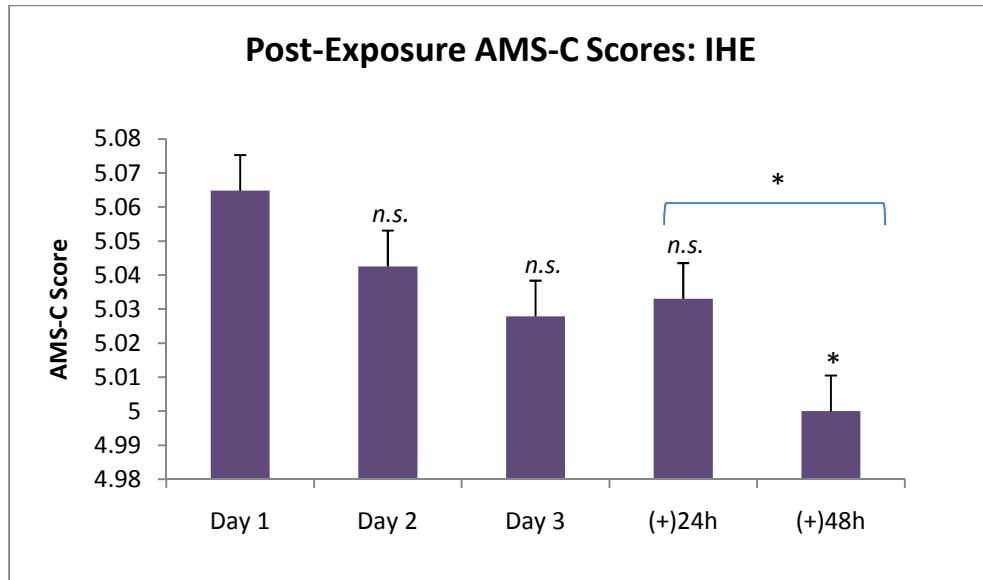


Figure 15: Post-Exposure AMS-C Scores: IHE. Despite the apparent trend, no significance was found between the day 1 post-exposure AMS-C score and the post-exposure AMS-C scores for day 2, day 3, +24h. There was a difference between day 1 and +48h and between +24h and +48h ($p < 0.05$).

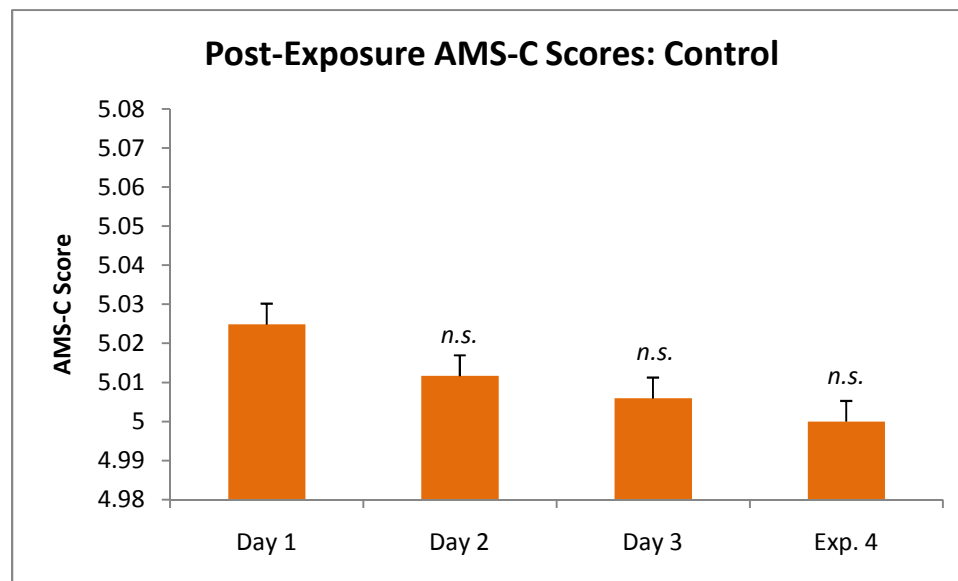


Figure 16: Post-Exposure AMS-C Scores: Control. No significance was found between the day 1 post-exposure AMS-C score and the post-exposure AMS-C scores for day 2, day 3, +24h or exposure 4.

	Day 1	Day 2	Day 3	Exp.4
Control : (n=3) mean <i>p-value</i>	5.05±0.05 ---	5.05±0.06 0.485	5.04±0.06 0.394	5.00±0.00 0.236
IHE: <u>+24h</u> (n=6) mean <i>p-value</i>	5.07±0.09 ---	5.04±0.04 0.188	5.03±0.04 0.072	5.03±0.04 0.178
<u>+48h</u> (n=5) mean <i>p-value</i>	5.07±0.09 ---	5.04±0.04 0.188	5.03±0.04 0.072	5.00±0.00 0.003*
<u>+24h vs. +48h</u> <i>p-value</i>				0.049*

No difference ($p>0.05$) was found for any of the post-exposure AMS-C scores compared to the day 1 value. In the IHE group a significant decrease was observed between day 1 and +48h ($p<0.01$), as well as between +24h and +48 h ($p<0.05$).

Lake Louise Score Questionnaire (LLSQ): Total Symptoms Score (TSS)

As a further measure of acute mountain sickness, the self-report component of the LLSQ was analyzed via the total symptoms score (TSS). The IHE group showed some significant variance between pre- and post-exposure TSS on day 1, but not other days except for the +24h group exposure 4 (figure 17). No significant variance was expressed in the control group, as shown in figure 18. Table 9 summarizes the mean pre- and post-exposure TSS for each group as well as the calculated p-values.

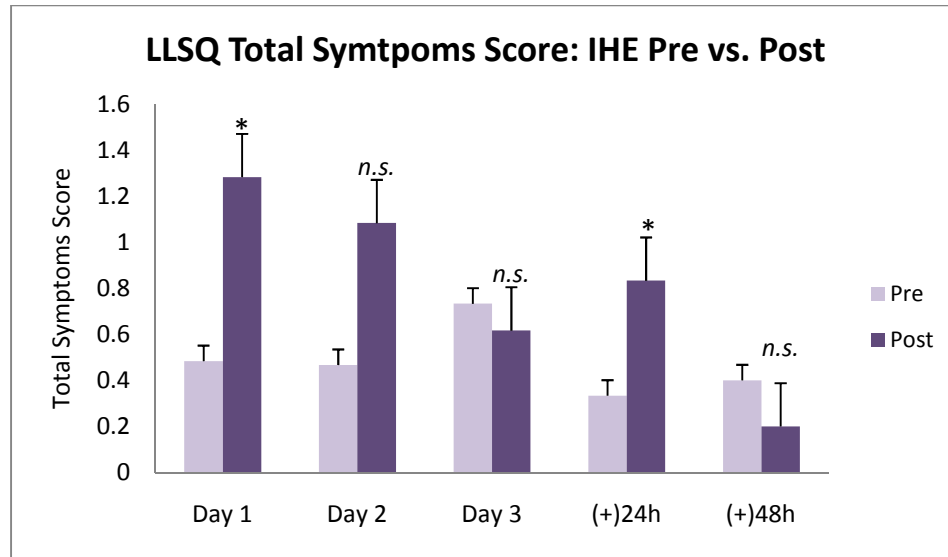


Figure 17: Pre vs. Post LLSQ Total Symptoms Score: IHE. A significant increase between pre- and post-exposure total symptoms score was observed in day 1 and in +24h ($p < 0.05$). There was no significance between pre- and post exposure for day 2, day 3 or for +48h ($p > 0.05$). In day 3 and +48h, there was an apparent decrease from pre- to post-exposure, though the difference was not significant.

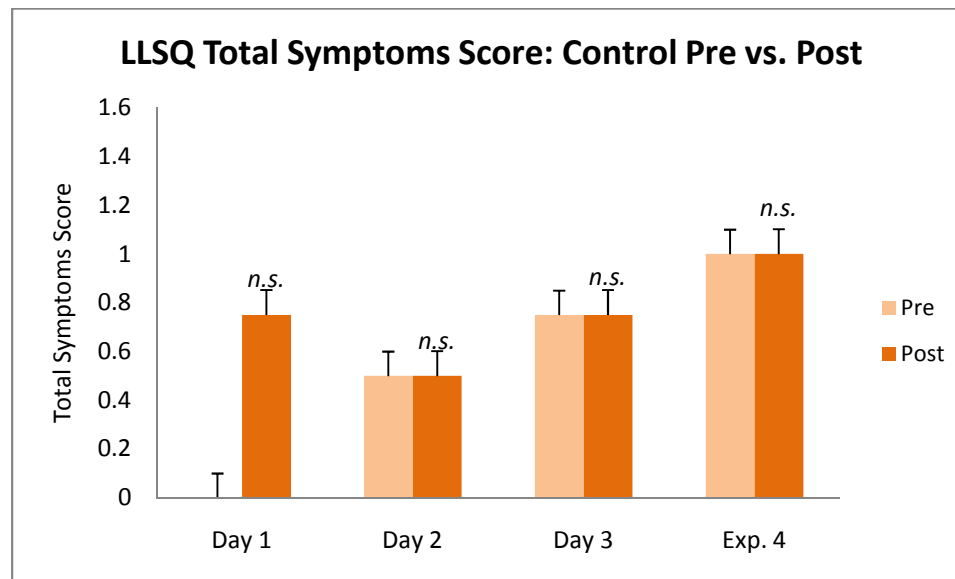


Figure 18: Pre vs. Post LLSQ Total Symptoms Score: Control. No significant variance was found between pre- and post-exposures for any control subjects ($p > 0.05$).

	<u>Control</u>		<u>IHE</u>	
	Total (n=3)		+24 (n=6)	+48 (n=5)
Day 1: pre	0.00±0.00		0.45±0.52	
post	0.67±0.58		1.27±1.10	
<i>p-value</i>	0.058		0.0190*	
Day 2: pre	0.33±0.58		0.45±0.52	
post	0.33±0.58		1.09±1.38	
<i>p-value</i>	no variance		0.083	
Day 3: pre	0.67±0.58		0.73±0.65	
post	0.67±0.58		0.64±0.81	
<i>p-value</i>	no variance		0.387	
Exp 4: pre	1.00±1.00		0.33±0.52	0.40±0.55
post	1.00±1.00		0.83±0.41	0.20±0.45
<i>p-value</i>	no variance		0.046*	0.272

Day 1 of the IHE group indicated a significant increase in LLQS TSS from pre- to post-exposure ($p < 0.05$). There was also a significant decrease observed from pre- to post-exposure in the +24h exposure ($p < 0.05$). No other significant variance occurred.

An analysis of the post-exposure total symptoms scores revealed no significance from day 1 to exposure 4 in the control group. The IHE group displayed a trend that appeared to approach significance (see figure 19 and table 10), but statistical significance was only observed between the IHE +48h exposure 4 and day 1 ($p < 0.05$), as well as between the +24h and the +48h exposure 4 ($p < 0.05$). The +48h score also varied significantly from the exposure 4 score of the Control group (figure 19 and table 10).

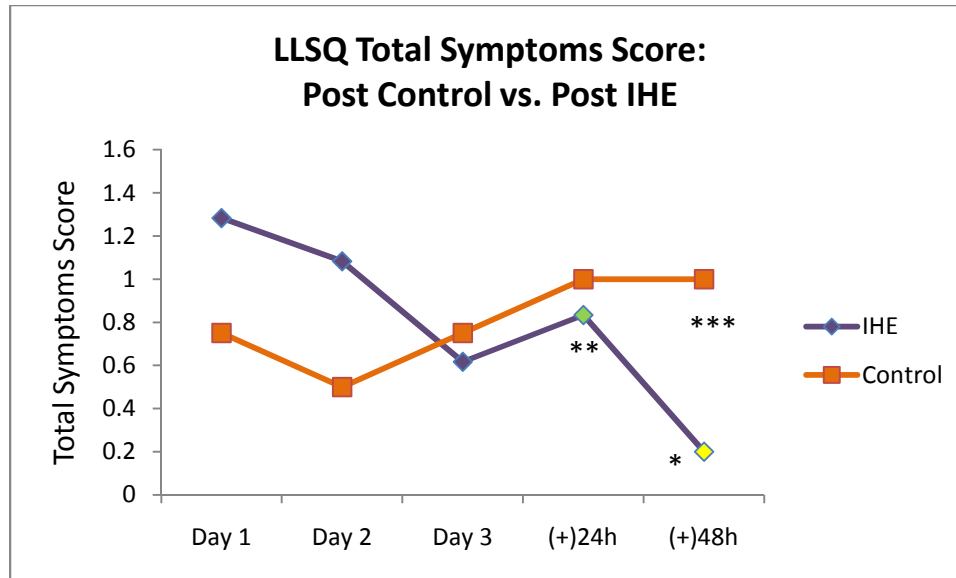


Figure 19: LLSQ TSS: IHE Post-Exposure Control vs. Post-Exposure IHE. No significance was observed from day 1 to exposure 4 in the Control group. A significant variance from the day 1 post-exposure TSS score was only observed in the IHE +48h group (indicated by *), as well as between the +24h and +48h scores (indicated by **) ($p < 0.05$). There was also a difference found between the exposure 4 Control TSS score and the IHE +48h score (indicated by ***) ($p < 0.05$). See table 10.

Table 10: Post-Exposure Total Symptoms Score vs. d1: Control and IHE					
	Day 1	Day 2	Day 3	Exp.4	
<u>Control</u> : (n=3) mean <i>p-value</i>	0.67±0.58 ---	0.33±0.58 0.259	0.67±0.58 0.500	1.00±0.00 0.187	
<u>IHE</u> : <u>+24h</u> (n=6) mean <i>p-value</i>	1.27±1.10 ---	1.09±1.38 0.368	0.64±0.81 0.069	0.83±0.41 0.184	
<u>+48h</u> (n=5) mean <i>p-value</i>	1.27±1.10 ---	1.09±1.38 0.368	0.64±0.81 0.069	0.20±0.45 0.029*	
+24h vs. +48h exp. 4 <i>p-value</i>				0.018*	
Control vs. IHE <i>p-value</i>	0.193	0.190	0.477	<u>+24h</u> 0.258	<u>+48h</u> 0.012*

No significance was observed from day 1 to exposure 4 in the Control group. A significant variance from the day 1 post-exposure TSS score was only observed in the IHE +48h group, as well as between the +24h and +48h scores ($p < 0.05$). There was also a difference found between the exposure 4 Control TSS score and the IHE +48h score ($p < 0.05$).

Mood State

Profile of Mood State (POMS): Total Mood Disturbance (TMD)

The analysis of total mood disturbance (TMD) as reported in the POMS indicated a significant increase in disturbance from pre- to post-exposure on day 1 for the IHE group ($p < 0.05$) (table 11). No significant change was observed on any other day for the IHE group (see figure 20) and no significant variance was observed on any day for the control group (figure 21).

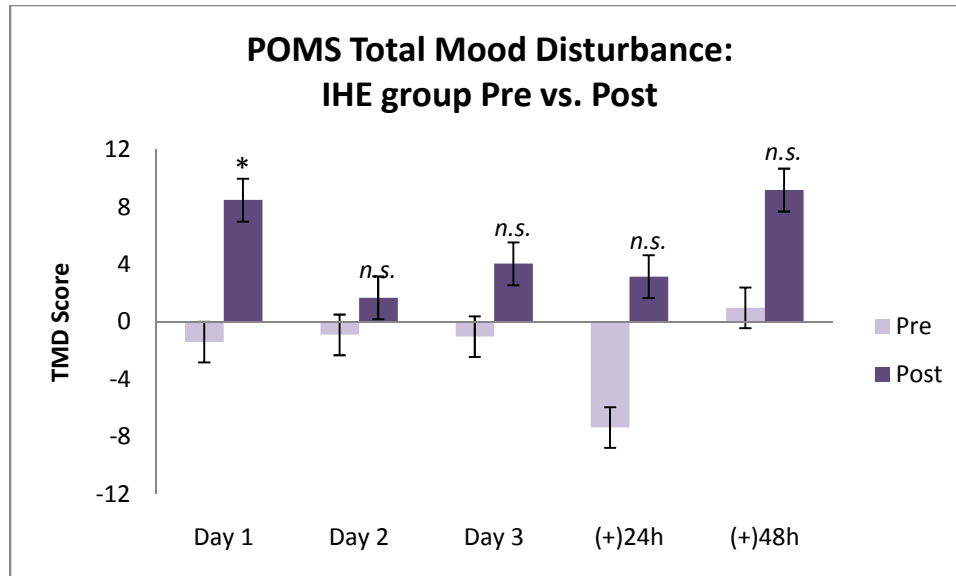


Figure 20: POMS TMD: IHE pre- vs. post-exposure scores. A significant increase in mood disturbance was seen in the post-exposure score versus the pre-exposure score on day 1 ($p < 0.05$). No other significance was observed on any other day.

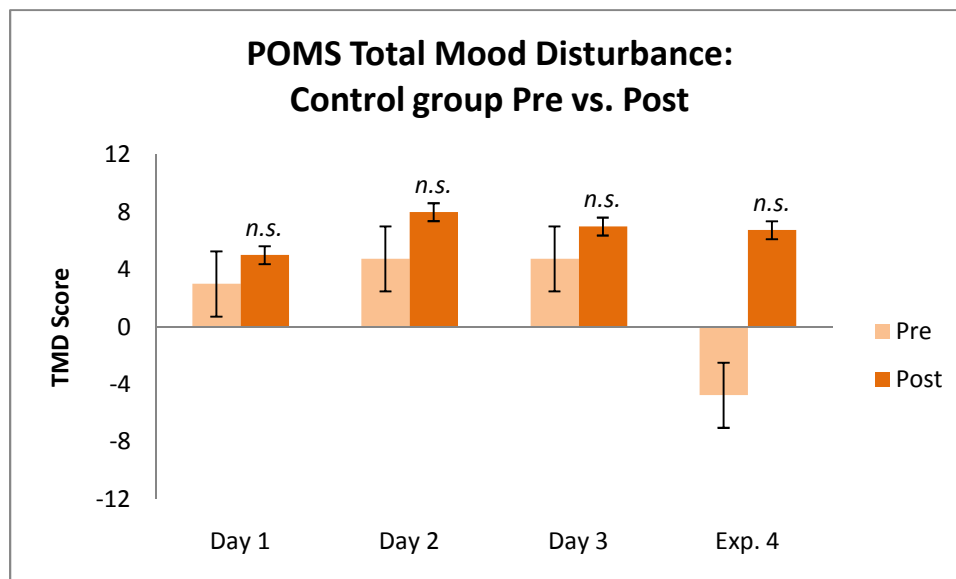


Figure 21: POMS TMD: Control pre- vs. post-exposure scores. No significant variance was found between pre- and post-exposure means of total mood disturbance on any day in the Control group.

	<u>Control</u>		<u>IHE</u>	
	Total (n=3)		+24 (n=6)	+48 (n=5)
Day 1: pre	6.33±24.9		-1.55±9.20	
post	6.00±6.93		8.18±16.3	
<i>p-value</i>	0.492		0.050*	
Day 2: pre	6.67±8.02		-1.09±12.23	
post	7.67±2.31		1.64±12.80	
<i>p-value</i>	0.423		0.3075	
Day 3: pre	3.67±12.1		-1.09±8.93	
post	6.67±6.11		3.82±16.6	
<i>p-value</i>	0.361		0.199	
Exp 4: pre	-5.67±7.23		-7.33±11.0	1.00±25.91
post	8.67±6.66		3.17±15.09	9.20±27.64
<i>p-value</i>	0.784		0.099	0.3207

Mean values of POMS TMD scores indicate no significant changes from pre- to post-exposure for both the control and the IHE groups except for on IHE day 1. P-values do appear to be closer to significance in the IHE group than in the control group.

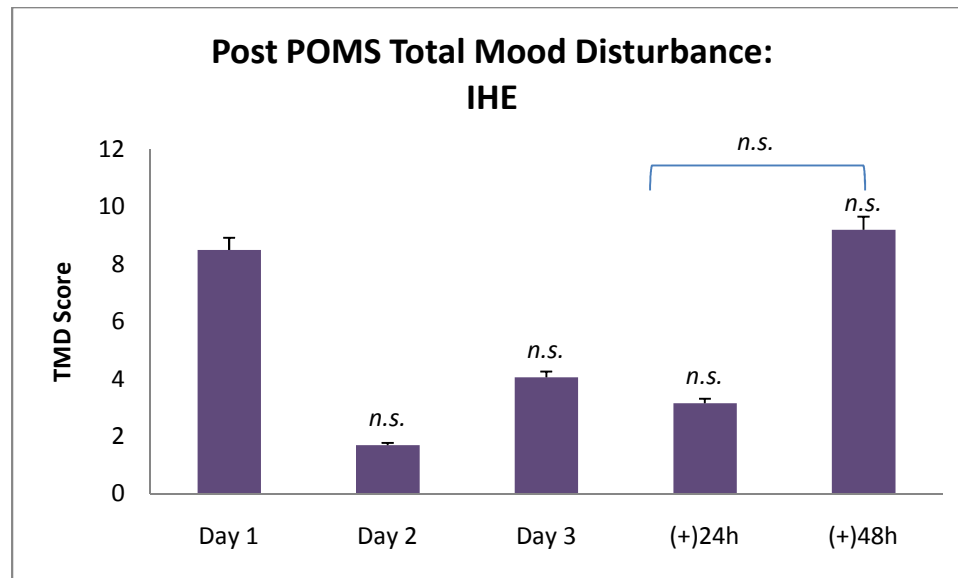


Figure 22: Post-Exposure POMS TMD scores: IHE. No significance was observed between the day 1 score and any other day. In addition, no significance was found between post-exposure TMD scores for the IHE +24h group and the IHE +48h group.

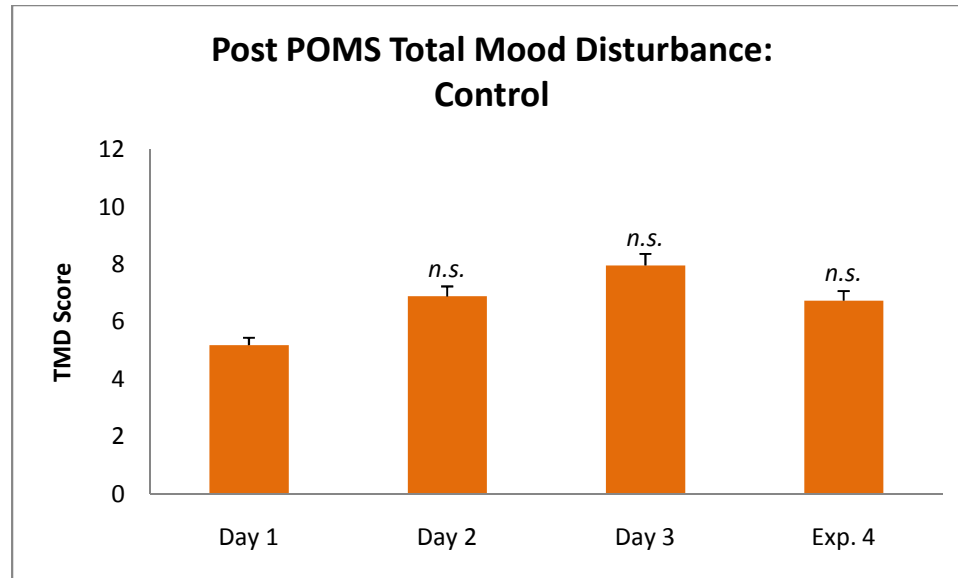


Figure 23: Post-Exposure POMS TMD scores: Control. No difference was found in post-exposure TMD scores between day 1 and any other exposure.

	Day 1	Day 2	Day 3	Exp.4		
Control : (n=3)						
mean	6.00±6.90	7.67±2.31	6.67±6.11	8.67±6.66		
<i>p-value</i>	---	0.356	0.453	0.328		
IHE:						
<u>+24h</u> (n=6)						
mean	8.18±16.3	12.8±1.64	3.82±16.6	3.17±15.1		
<i>p-value</i>	---	0.154	0.271	0.272		
<u>+48h</u> (n=5)						
mean	8.18±16.3	12.8±1.64	3.82±16.6	9.20±27.64		
<i>p-value</i>	---	0.154	0.271	0.464		
+24h vs. +48h exp. 4 <i>p-value</i>					<i>p=0.328</i>	
Control vs. IHE <i>p-value</i>	0.415	0.223	0.390	<u>+24h</u> 0.288	<u>+48h</u> 0.488	

No significant changes in post total mood disturbance (POMS) scores were observed from day 1 to the final exposure for any of the groups. In addition, there was no significance observed in the post-exposure TMD scores between the control and the exposure groups. Large standard deviations may be a result of a small sample size and a wide range of standard scores on the POMS questionnaire.

Feelings Profile: Total Mood Disturbance (TMD)

Self-reported total mood disturbance as measured by the feelings profile indicated no difference between day 1 values and any subsequent day in both the IHE and Control groups (figure 24 and table 13). There was also no notable difference between the mean TMD scores of the Control group as compared to the IHE groups.

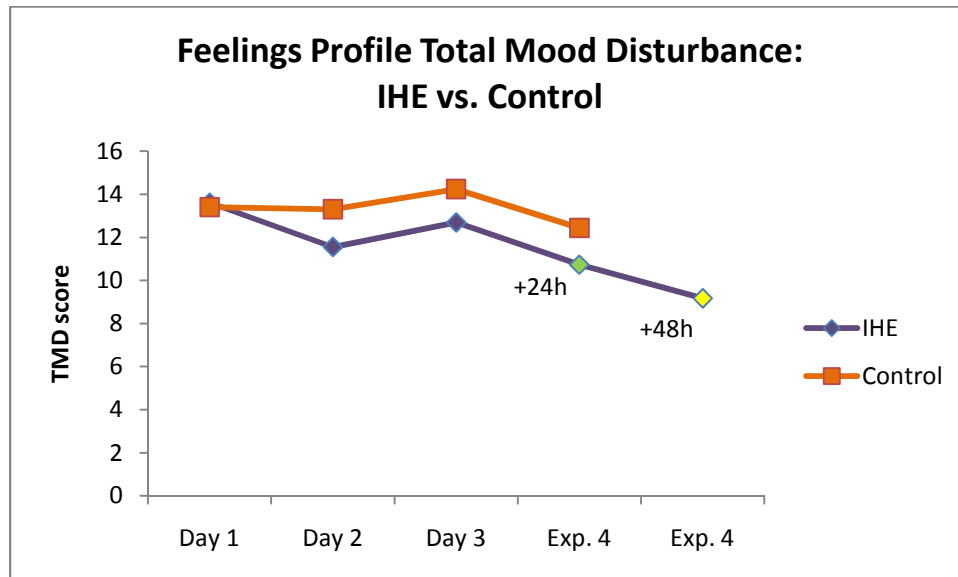


Figure 24: Feelings Profile TMD: IHE vs. Control. No significant variance was observed between day 1 scores and any other day for both the Control and the IHE groups. In addition, no notable difference was observed between Control and IHE values on any day.

Table 13: Feelings Profile TMD Scores vs. d1					
	Day 1	Day 2	Day 3	Exp.4	
<u>Control</u> : (n=3) mean <i>p-value</i>	13.1±2.73 ---	14.2±1.79 0.283	13.74±4.91 0.422	12.1±2.03 0.323	
<u>IHE</u> : <u>+24h</u> (n=6) mean <i>p-value</i>	13.4±4.48 ---	11.5±5.25 0.1875	12.5±5.45 0.344	10.7±1.90 0.097	
<u>+48h</u> (n=5) mean <i>p-value</i>	13.4±4.48 ---	11.5±5.25 0.1875	12.5±5.45 0.344	9.17±6.56 0.088	
+24h vs. +48h exp. 4 <i>p-value</i>				<i>p</i> =0.293	
Control vs. IHE <i>p-value</i>	0.456	0.200	0.365	<u>+24h</u> 0.178	<u>+48h</u> 0.249

No significance was found between day 1 and any other day Feelings Profile TMD scores for both the Control and the IHE group. In addition, no difference was observed between the Control and IHE mean scores for any day.

Conclusion

In conclusion, this study demonstrated that IHE sufficient to simulate an altitude of 4,300 m for 3h per day for 3 consecutive days resulted in acclimation to hypoxia that was sustained for at least 24h. $PEtCO_2$ was not different for the +24h group ($p=0.11$) whereas the +48h group showed a difference similar to that of the first (unacclimated) day ($P<0.01$). This indicates that any adaptation to hypoxia of the magnitude utilized in this study was lost between +24h and +48h after the last exposure. Even though treatment subjects (IHE +24h and IHE +48h groups) acted as their own controls by comparing post-tests to day 1 exposures, two control subjects were tested and found to not change in any of the parameters measured (HR, SaO_2 , $PEtCO_2$, Total Mood Disturbance, and AMS-C) during the experimental protocol. Other metrics measured supported the conclusion that adaptation to hypoxia was achieved during the 3h for 3d protocol (Mood State and AMS-C) but since exposure to a simulated altitude of 4,300 m was maintained for < 1 hour during the +24h and +48h exposures (exposure 4), there was not enough time (usually 1-6 hours of exposure) for AMS or mood state alterations to manifest.

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APPENDIX A

MEDICAL HISTORY

**To act as a volunteer in the research study:
PERSISTENCE OF ACCLIMATION TO NORMOBARIC
SIMULATED ALTITUDE**

Name: _____ Date: _____

Date of Birth: _____ Gender: M F

Contact Phone Number: _____

1. How often do you take part in physical activity or sports?
Not at all: _____. Days per week: _____.
2. What types of physical activity or sports do you usually participate in?
3. How would you compare yourself to others of your own gender and age in terms of physical ability and fitness?
Poor ____ Fair ____ Average ____ Above Average ____ Superior ____
4. Describe yourself in terms of physical activity:
Inactive ____ Moderately Active ____ Active ____ Very Active ____
5. Check which of the following respiratory problems you have or have had:

__Asthma	__Emphysema	__Bronchitis
__Hyperventilation (fast breathing)		__Chronic Cough
__Shortness of breath	__Other: _____	
__None of these		
6. Do you presently have any medical problems? Y N

If yes, please indicate the nature of the problem and what therapy and/or medication you are taking:

7. Have you been treated over the past 5 years for anything other than minor illnesses? Y N

If yes, please indicate the nature of the injury or illness, therapy, and length of hospitalization, if appropriate.

8. Have you ever had or have you now?

- | | | |
|---|--|--|
| <input type="checkbox"/> Anemia | <input type="checkbox"/> Sickle cell trait | <input type="checkbox"/> Sickle cell disease |
| <input type="checkbox"/> Hypertension | <input type="checkbox"/> Diabetes | <input type="checkbox"/> Tuberculosis |
| <input type="checkbox"/> Head injury | <input type="checkbox"/> Bad headache | <input type="checkbox"/> Unconsciousness |
| <input type="checkbox"/> Sinus problems | <input type="checkbox"/> Nose/throat trouble | <input type="checkbox"/> Ear problems |
| <input type="checkbox"/> Hearing loss | <input type="checkbox"/> Ringing in the ears | <input type="checkbox"/> Eye trouble |
| <input type="checkbox"/> Vision problems | <input type="checkbox"/> Thyroid trouble | <input type="checkbox"/> Chronic colds |
| <input type="checkbox"/> Nervous trouble | <input type="checkbox"/> Trouble sleeping | <input type="checkbox"/> Allergies |
| <input type="checkbox"/> Dizziness/Fainting | <input type="checkbox"/> Stomach problems | <input type="checkbox"/> Stroke |
| <input type="checkbox"/> Adverse reaction to
medications | <input type="checkbox"/> Heart disease | <input type="checkbox"/> Vascular disease |
| <input type="checkbox"/> Nut allergy | <input type="checkbox"/> Thalassemia | <input type="checkbox"/> Family history of
heart attack prior to
the age of 50 |
| <input type="checkbox"/> Prior history of seizures | <input type="checkbox"/> Food allergy | |

9. Diet/Medications:

Caffeinated coffee (cups per day): _____.

Caffeinated tea (cups per day): _____.

Caffeinated soft drinks or sodas (cans per day): _____.

Cigarettes (packs per day): _____.

Cigar (number per day): _____.

Pipe (number per day): _____.

Prescription drugs (list if applicable and state reason for use):

APPENDIX B

Volunteer Informed Consent For the research project titled:

PERSISTENCE OF ACCLIMATIZATION TO NORMOBARIC SIMULATED HIGH ALTITUDE

I, _____, Date: _____, having full capacity to consent and understanding that I must be at least 18 years old to participate, having attained my _____ birthday, do hereby volunteer to participate in a research study titled: "Persistence of acclimatization to normobaric simulated high altitudes" under the direction of Kenneth W. Kambis, Ph.D., Professor of Kinesiology at The College of William and Mary, Williamsburg, Virginia 23187 conducted in The Jack Borgenicht Altitude Physiology Research Facility, The College of William and Mary. The implications of my voluntary participation; duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by Professor Kambis, Contact Phone Number: 757-221-2779. I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights or study-related injury, I may contact the Chair of the Protection of Human Subjects Committee at The College of William and Mary, Michael Deschenes, Ph.D., Contact Phone Number: 757-221-2778. I understand that I may at any time during the course of the study revoke my consent and withdraw from the study without further penalty of loss of benefits. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

RESEARCH TEAM:

Kenneth W. Kambis, Ph.D., Professor of Kinesiology; Alastair Connell, M.D. Clinical Professor of Kinesiology; and, Reina Chamberlain, undergraduate honors student at The College of William and Mary. Other student and/or faculty research assistants as identified by the PI.

RESEARCH LOCATION:

The Jack Borgenicht Altitude Physiology Research Facility is located in Adair Hall, Room 108 on the campus of The College of William and Mary in Williamsburg, Virginia.

The facility consists of a normobaric hypoxic room within which the partial pressure of oxygen can be finely controlled to simulate atmospheres found at altitudes from sea-level to 18,000 feet.

OVERVIEW OF STUDY:

The study will be performed in two phases: I) resting exposure to either sea level or up to 14,000 ft (4,300 meters) simulated altitudes for three (3) hours for up to five consecutive days, after which you will; II) be exposed to 14,000 ft (4,300 m) for three (3) hours either 24 hours after completion of phase I or 48 hours after completion of phase I at which time we will conduct post-testing for comparison with baseline data. You may read, study, watch DVD's or work at your computer while in the altitude chamber. You cannot sleep or exercise during any of the altitude exposures. The time commitment for this study is considerable and will require about 15 hours of your time over approximately 6 days. We will work within your personal and school schedule as much as is possible. All aspects of this study will be conducted in the Jack Borgenicht Altitude Physiology Research Facility located in Adair Hall Room 108 on the campus of The College of William and Mary in Williamsburg, Virginia.

If you have ANY questions, before the study starts or after the study starts, the research staff EXPECTS you to ask us. Specifically, call or E-mail the Principal Investigator (Dr. Kenneth Kambis, Williamsburg, VA 757-221-2779; kwkamb@wm.edu). If he cannot answer your questions, he likely will be able to provide you with the name of someone or an organization that will.

STUDY PURPOSES:

There are two primary purposes of this research study: 1) Determine how intermittent short (3-hour) exposure to altitudes of approximately 14,000 feet (4,300 m) will affect your ability to adapt to high altitude, and 2) how long these adaptations persist. We will then input the collected data into a database whose results will be used to predict outcomes such as how much Acute Mountain Sickness (AMS), negative mood state alterations, and other altitude illnesses may be reduced if people are exposed to IHE prior to going to high altitudes.

ELIGIBILITY TO PARTICIPATE

We ask that you read the entire document, ask questions, and take the time to discuss with us anything that you do not understand or that concerns you with the study.

To participate you must:

Be a non-smoking healthy man or non-pregnant woman between the ages of 18 and 35 years.

Not have been born at an altitude of greater than 1,500 meters (4,500 feet).

Not have traveled to altitudes greater than 5,000 feet for more than 2 days within the past 6 months.

If you meet the eligibility requirements above, you will be medically screened. The screening will consist of a medical history and review of your medical history by medical personnel or their designates. Volunteers with evidence of anemia of hemoglobin S ("sickle cell") will be excluded. Volunteers with evidence of any physical, mental, and/or medical conditions that would make the proposed study more hazardous will be excluded.

There will be a total of 24 volunteers that will participate in this study.

SPECIFIC STUDY PROCEDURES:

The first time you participate in a test, the main goal will be to familiarize you with the test and the staff who are performing the test.

1. Acute Mountain Sickness (AMS)

Acute Mountain Sickness will be assessed by questionnaires, using pencil and paper. Just after you complete the questionnaire, a padded sensor ("finger oximeter") will be placed over your finger tip to measure how much oxygen is in your blood (it shines a light through your finger). Each entire AMS assessment and oxygen measurement will take a total of less than 10 minutes to complete.

2. Mood

The mood scale questionnaires are designed to assess your emotional state at the moment you take the questionnaire. The mood scale is a paper and pencil questionnaire (65 items) that you will be given twice each day. In addition, you will be given a shortened version ("Feelings Profile" a 19-item questionnaire administered via touch-screen) up to 12 times per day. The longer version takes less than 5 minutes to complete and the shorter version takes less than 1 minute to complete.

3. Body Weight

Body weight will be measured each day before and after your stay in the altitude chamber.

4. Oxygen saturation of hemoglobin

A padded sensor that shines a light through your finger will be placed over your finger tip to determine how much oxygen is being transported in your bloodstream.

5. Resting ventilation

Before and after each altitude exposure, you will be asked to sit quietly (no sleeping) while breathing into a mouthpiece. The mouthpiece is connected via plastic hose to a gas analyzer that will measure the amount of CO₂ that you are exhaling. This test requires about 12 minutes to complete.

POTENTIAL RISKS AND HAZARDS

The potential risks to you from participation in this study include the risks associated with altitude exposure and the risks that are part of the test procedures, measurements, and equipment used in the study.

Risks Associated with Altitude Exposure:

The risks associated with the reduced level of oxygen imposed by this study include Acute Mountain Sickness (AMS). However, because the length of exposure is short (no more than 3 hours), the risk of you developing severe AMS is not great. Nevertheless, you may still develop a headache and nausea, but these symptoms will greatly diminish or disappear over the duration of the study. An investigator will be present to take you to a lower altitude, if necessary. Water in the lungs (High Altitude Pulmonary Edema – HAPE) rarely occurs even in people who are not used to living at altitude. Even rarer is High Altitude Cerebral Edema (HACE). If either of these responses develops, you will be treated appropriately with oxygen and immediately be taken to a lower altitude. Hospitalization is possible but unlikely. High Altitude Retinal Hemorrhage (HARH) is a benign condition from which recovery is complete within a few days of returning to a lower altitude. Although HARH frequently occurs at very high and extreme altitudes, it is unlikely to occur at elevations used in this study.

Risks Associated with Test Equipment:

All instruments to be used in testing will be operated by trained personnel.

Mental Function:

There are no risks associated with mood state or AMS questionnaires.

Resting Ventilation:

There are no risks associated with taking a resting ventilation test.

STUDY COMMITMENT:

It is important that you understand this study and the commitment it will require of you. You are encouraged to ask any questions necessary before or after volunteering. Because of the time and expense involved in this study, if you volunteer, we would like you to be reasonably committed to completing the study. However, you have the right to withdraw from the study at any time without adverse consequences or prejudice.

Other Reasons for Your Leaving the Study:

The Principal Investigator may stop your participation without your permission. Your participation may be stopped if you are unwilling or unable to complete the study testing tasks. The Principal Investigator may also stop your participation if you become ill, injured or believes that continuing may not be in your best interest.

BENEFITS TO YOU:

There are no direct benefits to you for participating in this study as a volunteer, except the knowledge of how well you performed on the tests that you participate in. At the conclusion of your experiment, you will be paid \$50.00 for your participation in the study.

INJURY OR SICKNESS NOTIFICATION:

If you become sick or injured as a result of this study, you should immediately notify the Principal Investigator associated with the study.

EMERGENCY MEDICAL CARE:

In the event of a medical emergency, the emergency medical services (EMS) system will be activated by telephone (911), and while awaiting the arrival of EMS, trained personnel (CPR trained) will provide basic life support and first aid. Neither the researchers, the Department of Kinesiology, or The College of William and Mary can assume responsibility for any medically untoward outcome. While emergency first aid may be provided by the staff and/or the Student Health Service, any subsequent medical care will be the participant's responsibility.

INVITATION FOR QUESTIONS:

If you have any questions, we expect you to ask us. If you have any additional questions later, further information about the study can be obtained from Dr. Kenneth W. Kambis (757/221-2779). You may report dissatisfactions with any aspect of this experiment to the Chair of the Protection of Human Subjects Committee, Dr. Michael Deschenes, (757) 221-2778.

YOUR SIGNATURE INDICATES THAT YOU HAVE READ AND UNDERSTAND THE ABOVE INFORMATION, THAT YOU HAVE DISCUSSED THIS STUDY WITH THE PERSON OBTAINING CONSENT, THAT YOU HAVE DECIDED TO PARTICIPATE BASED ON THE INFORMATION PROVIDED, AND THAT A COPY OF THIS FORM HAS BEEN GIVEN TO YOU.

Signature Date

Printed Name

Person obtaining consent Date

Printed Name

Signature of Witness Date

Printed Witness Name

THIS PROJECT WAS APPROVED BY THE COLLEGE OF WILLIAM AND MARY PROTECTION OF HUMAN SUBJECTS COMMITTEE (Phone: 757-221-2778) ON 2008-07-10 AND EXPIRES ON 2009-07-10.

APPENDIX C

JD

DATE _____ SEX: Male (M) Female (F)

Below are words that describe feelings and moods people have. Please read EVERY word carefully. Then fill in ONE circle under the answer to the right which best describes how you are feeling RIGHT NOW.

Suppose the word is happy. Mark the one answer which is closest to how you are feeling RIGHT NOW.

The numbers refer to these phrases.

- ① = Not at all
- ① = A little
- ② = Moderately
- ③ = Quite a bit
- ④ = Extremely

		Not at all A little Moderately Quite a bit Extremely	Not at all A little Moderately Quite a bit Extremely
T			
	1. Friendly	① ② ③ ④	21. Hopeless
	2. Tense	① ② ③ ④	22. Relaxed
			23. Unworthy
			24. Spiteful
			25. Sympathetic
			26. Uneasy
D	3. Angry	① ② ③ ④	27. Restless
	4. Worn out	① ② ③ ④	28. Unable to concentrate
			29. Fatigued
A	5. Unhappy	① ② ③ ④	30. Helpful
	6. Clear-headed	① ② ③ ④	31. Annoyed
	7. Lively	① ② ③ ④	32. Discouraged
	8. Confused	① ② ③ ④	33. Resentful
V	9. Sorry for things done .	① ② ③ ④	34. Nervous
	10. Shaky	① ② ③ ④	35. Lonely
			36. Miserable
F	11. Listless	① ② ③ ④	37. Muddled
	12. Peeved	① ② ③ ④	38. Cheerful
			39. Bitter
C	13. Considerate	① ② ③ ④	40. Exhausted
	14. Sad	① ② ③ ④	41. Anxious
	15. Active	① ② ③ ④	42. Ready to fight
	16. On edge	① ② ③ ④	43. Good natured
	17. Grouchy	① ② ③ ④	44. Gloomy
	18. Blue	① ② ③ ④	
	19. Energetic	① ② ③ ④	
	20. Panicky	① ② ③ ④	
			45. Desperate
			46. Sluggish
			47. Rebellious
			48. Helpless
			49. Weary
			50. Bewildered
			51. Alert
			52. Deceived
			53. Furious
			54. Efficient
			55. Trusting
			56. Full of pep
			57. Bad-tempered
			58. Worthless
			59. Forgetful
			60. Carefree
			61. Terrified
			62. Guilty
			63. Vigorous
			64. Uncertain about things
			65. Bushed
			MAKE SURE YOU HAVE ANSWERED EVERY ITEM

APPENDIX D

ENVIRONMENTAL SYMPTOMS QUESTIONNAIRE III (ESQ-III)

The College of William and Mary
Jack Borgenicht Altitude Physiology Research Facility

Volunteer # _____ **Date:** _____ **Time:** _____
(month/day/ year) (24 hour clock)

Instructions: Circle the number of each item to indicate HOW YOU FEEL RIGHT NOW. Please answer every item. If you did not have the symptom, circle zero (Not at all).

		Not at all		Somewhat		Quite a bit	
		Slight		Moderate		Extreme	
1.	I feel lightheaded	0	1	2	3	4	5
2.	I have a headache	0	1	2	3	4	5
3.	I feel sinus pressure	0	1	2	3	4	5
4.	I feel dizzy	0	1	2	3	4	5
5.	I feel faint	0	1	2	3	4	5
6.	My vision is dim	0	1	2	3	4	5
7.	My coordination is off	0	1	2	3	4	5
8.	I'm short of breath	0	1	2	3	4	5
9.	It is hard to breathe	0	1	2	3	4	5
10.	It hurts to breathe	0	1	2	3	4	5
11.	My heart is beating fast	0	1	2	3	4	5
12.	My heart is pounding	0	1	2	3	4	5
13.	I have chest pain	0	1	2	3	4	5
14.	I have chest pressure	0	1	2	3	4	5
15.	My hands are shaking or trembling	0	1	2	3	4	5
16.	I have a muscle cramp	0	1	2	3	4	5
17.	I have stomach cramps	0	1	2	3	4	5
18.	My muscles feel tight or stiff	0	1	2	3	4	5
19.	I feel weak	0	1	2	3	4	5
20.	My legs or feet ache	0	1	2	3	4	5
21.	My hands, arms, or shoulders ache	0	1	2	3	4	5
22.	My back aches	0	1	2	3	4	5

23.	I have a stomach ache	0	1	2	3	4	5
24.	I feel sick to my stomach (nauseous).	0	1	2	3	4	5
25.	I have gas pressure	0	1	2	3	4	5
		Not at all	Slight	Somewhat	Moderate	Quite a bit	Extreme
26.	I have diarrhea	0	1	2	3	4	5
27.	I'm constipated	0	1	2	3	4	5
28.	I have to urinate <u>more</u> than usual	0	1	2	3	4	5
29.	I have to urinate <u>less</u> than usual	0	1	2	3	4	5
30.	I feel warm	0	1	2	3	4	5
31.	I feel feverish.	0	1	2	3	4	5
32.	My feet are sweaty	0	1	2	3	4	5
33.	I'm sweating all over	0	1	2	3	4	5
34.	My hands are cold	0	1	2	3	4	5
35.	My feet are cold	0	1	2	3	4	5
36.	I feel chilly	0	1	2	3	4	5
37.	I'm shivering	0	1	2	3	4	5
38.	Parts of my body feel numb	0	1	2	3	4	5
39.	My skin is burning or itchy	0	1	2	3	4	5
40.	My eyes feel irritated	0	1	2	3	4	5
41.	My vision is blurry	0	1	2	3	4	5
42.	My ears feel blocked up	0	1	2	3	4	5
43.	My ears ache	0	1	2	3	4	5
44.	I can't hear well	0	1	2	3	4	5
45.	My ears are ringing	0	1	2	3	4	5
46.	My nose feels stuffed up	0	1	2	3	4	5
47.	I have a runny nose	0	1	2	3	4	5
48.	I've been having nose bleeds	0	1	2	3	4	5
49.	My mouth is dry	0	1	2	3	4	5
50.	My throat is sore	0	1	2	3	4	5
51.	I've been coughing	0	1	2	3	4	5
52.	I've lost my appetite	0	1	2	3	4	5
53.	I feel sick	0	1	2	3	4	5
54.	I feel hungover	0	1	2	3	4	5
55.	I'm thirsty	0	1	2	3	4	5

56.	I feel tired	0	1	2	3	4	5
57.	I feel sleepy	0	1	2	3	4	5
58.	I feel wide awake (can't sleep well)	0	1	2	3	4	5
		Not at all	Slight	Somewhat	Moderate	Quite a bit	Extreme
59.	My concentration is off	0	1	2	3	4	5
60.	I'm more forgetful than usual	0	1	2	3	4	5
61.	I feel worried or nervous	0	1	2	3	4	5
62.	I feel irritable	0	1	2	3	4	5
63.	I feel restless	0	1	2	3	4	5
64.	I'm bored.	0	1	2	3	4	5
65.	I feel depressed	0	1	2	3	4	5
66.	I feel alert	0	1	2	3	4	5
67.	I feel good	0	1	2	3	4	5
68.	I am hungry	0	1	2	3	4	5

THANK YOU!

APPENDIX E

LAKE LOUISE SCORE QUESTIONS: ID: _____ Date: _____ Time: _____

Symptom	Definition	Score
<u>Self-Report Questionnaire</u>		
1. Headache:	None at all	0
	A mild headache	1
	Moderate headache	2
	Severe headache, incapacitating	3
2. Gastrointestinal Symptoms:	No gastrointestinal symptoms	0
	Poor appetite or nausea	1
	Moderate nausea or vomiting	2
	Severe nausea and vomiting, incapacitating	3
3. Fatigue and/or weakness:	Not tired or weak	0
	Mild fatigue/weakness	1
	Moderate fatigue/weakness	2
	Severe fatigue/weakness, incapacitating	3
4. Dizziness/lightheadedness:	Not dizzy	0
	Mild dizziness	1
	Moderate dizziness	2
	Severe dizziness, incapacitating	3
5. Difficulty sleeping:	Slept as well as usual	0
	Did not sleep as well as usual	1
	Woke up many times, poor night's sleep	2
	Could not sleep at all	3

APPENDIX F

FEELINGS PROFILE – A (971)

NAME: _____ ID Number: _____

Below is a list of words that describes feelings people have. Please read each one carefully. Then circle the number to the right which best describes **HOW YOU ARE FEELING RIGHT NOW**. The numbers refer to the following descriptive phrases:

- 1 = Not at all**
2 = A little
3 = Moderately
4. Quite a bit
5. Extremely

1.	Friendly	1	2	3	4	5
2.	Tense	1	2	3	4	5
3.	Sad	1	2	3	4	5
4.	Angry	1	2	3	4	5
5.	Active	1	2	3	4	5
6.	Fatigued	1	2	3	4	5
7.	Bewildered	1	2	3	4	5
8.	Shaky	1	2	3	4	5
9.	Hopeless	1	2	3	4	5
10.	Furious	1	2	3	4	5
11.	Energetic	1	2	3	4	5
12.	Exhausted	1	2	3	4	5
13.	Unable to Concentrate	1	2	3	4	5
14.	Nervous	1	2	3	4	5
15.	Unworthy	1	2	3	4	5
16.	Bad-tempered	1	2	3	4	5
17.	Full of Pep	1	2	3	4	5
18.	Bushed	1	2	3	4	5
19.	Forgetful	1	2	3	4	5