PHYSIOLOGICAL DIFFERENCES BETWEEN FIT AND UNFIT COLLEGE-AGE MALES DURING EXERCISE IN NORMOBARIC HYPOXIA

A dissertation submitted to the Kent State University College of Education, Health, and Human Services in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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December, 2013
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Previous research suggests that physical activity may result in decreases in arterial saturation (SaO$_2$) and cerebral blood flow when exposed to a low oxygen environment between aerobically fit and unfit males. **Purpose:** The purpose of this study was to determine differences in SaO$_2$, cerebral blood flow, minute ventilation ($V_E$), and blood lactate between fit and unfit young males during exercise in hypoxia compared to normoxia. **Methods:** Apparently healthy college age males took part in two trials consisting of normobaric normoxia and normobaric hypoxia (12% oxygen). Fit (n = 3; $VO_{2max} = 51.5$ ml kg$^{-1}$ min$^{-1}$ ± 3.1) and Unfit (n = 3; $VO_{2max} = 34.4$ ml kg$^{-1}$ min$^{-1}$ ± 5.6) males cycled at 50% of their altitude adjusted $VO_{2max}$ (-26% of normoxia $VO_{2max}$) for one hour after a two-hour baseline. **Results:** SaO$_2$, cerebral blood flow, and RER were significantly decreased during hypoxia in all subjects ($P < 0.05$), but did not differ between groups. An interaction showed that Fit subjects had a higher SaO$_2$ during exercise in hypoxia ($P < 0.05$). $V_E$ and lactate was greater during hypoxia ($P < 0.05$). The Fit group demonstrated a higher $V_E$ during exercise in hypoxia ($P < 0.05$). No differences in blood lactate were found between the two groups. **Conclusion:** The data suggests that when exposed to hypoxia aerobically unfit males may demonstrate decrements in oxygen utilization which may lead to decreases in physical activity and/or performance.
ACKNOWLEDGEMENTS

I could literally write an entire dissertation on how thankful I am while including all the people in my life that have helped me get to this point. However, a one-way analysis of variance has revealed there is a significantly low page number length of the acknowledgements section compared to the length of the dissertation overall. Therefore, my space is limited.

First thing I want to say is that I would like to apologize to myself for not completing this dissertation sooner. Although I have learned great skills in other areas during graduate school, there were times where I should have put more time into this paper. However, I feel lucky to have started my career and will continue to learn about research and exercise physiology.

I would like to thank my undergraduate advisor, Dr. Wright, and my graduate advisor, Dr. Glickman, as well as Dr. Barkley and Dr. Ganong for providing me with the much-needed knowledge and guidance.

This goal would not have been reached without some great friends I’ve made along the way. Thank you EJ, Muller, Chul, and Brian.

There is a strong positive correlation in my life when it comes to family versus success. Thank you to my parents and my sister for providing me the support needed when things were good and not so good.

Last, and most importantly, Thank You, Amber!
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CHAPTER I
INTRODUCTION

Oxygen is the most important element used by the human body for energy utilization. Lack of oxygen (hypoxia) can occur from diseases of the airway (i.e. chronic obstructive pulmonary disease and sleep apnea) or from the environment. Boyle’s Law states that volume is inversely proportional to pressure. At altitude, the partial pressure of oxygen is decreased; therefore, the same volume of air is less comprised of oxygen than at a lower altitude. Decrease in barometric pressure as well as the partial pressure of oxygen will hinder gas exchange. The human body attempts to compensate for the limited oxygen availability by cardiovascular responses (increased heart rate and cardiac output) and pulmonary responses (increased rate of breathing and volume). These alterations are an attempt to increase the amount of oxygen delivery to the body’s tissues for physical activity.

These increases will continue until the individual becomes acclimatized to the altitude. However, without acclimatization to low oxygen environments acute physiological and psychological effects ensue. An increase in pulmonary ventilation continues (up to about two weeks after arrival) due to the peripheral chemoreceptors’ responses to hypoxia (Bartch and Saltin, 2008).

Acute mountain sickness (AMS) is a common symptom of hypoxic environment. AMS symptoms include nausea, vomiting, dizziness, and sleep disturbances. The cause of AMS is not clearly understood. However, the increase in cranial pressure followed by increase in cerebral blood flow may elicit AMS, and potentially develop to cerebral
edema (Fagenholz et al., 2009). During hypoxia low arterial oxygen saturation (SaO$_2$) induces cardiac output and vasodilation, and it may increase cerebral blood flow and pressure (Cohen, et al., 1967 and Buck, et al., 1998).

Exercise in a hypoxic environment can further elicit physiological adaptations. Research suggests that physical activity may result in further decreases in arterial oxygenation, and it consequently increases the incidence and severity of AMS (Roch et al., 2000). Furthermore, it has been shown that maximal cycling at altitude will further decrease SaO$_2$ due to the decrement in the alveolar pressure of O$_2$ (Gore et al., 1996). While cycling in normobaric hypoxia following two hours of baseline, Glickman et al. (2010) also demonstrated that cerebral oxygenation was significantly decreased in middle-aged males during cycling exercise when compared to resting in normobaric hypoxia. Exercise may also cause an increase cerebral blood flow which will continue to rise as the intensity of exercise increases. However, even though exercise intensity may further increase cerebral blood flow, it may progressively decrease to baseline values (Ogoh and Ainslie, 2009).

While exercising in hypoxia perceived discomfort is increased at the same intensity as in normoxia. Romer et al. (2007) demonstrated that limb discomfort was significantly increased between exercising in hypoxia versus normoxia. This may also lead to a significant decrease in time to exhaustion in the hypoxic condition. Thus, leg discomfort may lead to an increase in perceived exertion during exercise in hypoxia.

Physical fitness (i.e., aerobic training) is a major factor that contributes to how the individual responds to a given environmental stressor that they are not acclimated to.
Hypoxic conditions have been shown to cause the body to react differently between trained and untrained individuals. Mollard et al. (2007) examined maximum heart rate ($HR_{\text{max}}$) and $SaO_2$ between endurance trained and untrained males at two separate altitudes. Their research demonstrated that $HR_{\text{max}}$ and $SaO_2$ were significantly lower in the trained subjects than untrained subjects. In a similar study, Woorons et al. (2007) also demonstrated a significant difference in $SaO_2$ between trained and untrained college-aged males while cycling in normoxia and hypoxia. The data showed that the $SaO_2$ was significantly lower in the trained group compared to the untrained group. It has been suggested that the causes of this decrement may be due to the increased response of trained individuals to hypoxia (i.e. increased ventilation) (Mollard et al., 2007, and Woorons et al., 2007). Increased cardiac output (Q) due to training and increased physical fitness (aerobic training) may also play a role in the decrease in $SaO_2$ (Bartch and Saltin, 2008). The increased Q will lead to more blood reaching the tissues of the body and releasing oxygen more rapidly than those with lower Q such as aerobically untrained individuals.

As stated previously, $O_2$ saturation can be used to predict symptoms of AMS due to the vasodilation. Therefore, the greater decrease in $SaO_2$ in trained individuals could raise speculation of whether trained individuals will experience AMS symptoms more so than their untrained counterparts.

**Statement of the Problem**

Previous studies have examined differences among trained and untrained individuals exercising in hypoxia. Research data suggested that there are differences
between the two groups (i.e., fit and unfit) in SaO$_2$ and HR. However, the changes within cerebral oxygenation, SaO$_2$ during one hour of cycling in normobaric hypoxia (as well as normoxia) following two hours of baseline between the trained and untrained college-aged males has been not been elucidated.

**Purpose of the Study**

The purpose of the present study was to evaluate the physiological differences (i.e. cerebral blood flow, arterial saturation, respiratory responses, and blood lactate) between aerobically fit and unfit college age males in response to exercise in normobaric hypoxia versus normobaric normoxi
CHAPTER II

REVIEW OF LITERATURE

HYPOXIA

Hypoxia is a physiological state defined as a reduction in the ability of oxygen to reach the tissues of the body. Preservation of adequate oxygen supply is critical for physiological and psychological functions of the human body. Therefore, the respiratory system systematically delivers oxygen from the ambient air to the lungs, heart, arteries, and the tissues and cells of the body (Cheung, 2010), and the internal organs require adequate oxygen supply for energy utilization. However, the required level of oxygen can be altered by pathological or environmental changes such as altitude, chronic lung disease, asthma and sleep apnea (Ogoh and Ainslie, 2009), and a disruption of balance between oxygen supply and oxygen demand may lead to hypoxic condition.

Furthermore, hypoxia may be induced via exposure to environmental conditions that impede on the body’s ability to transfer oxygen from ambient air to bodily tissues. At sea-level, \( \text{PO}_2 \) (Partial Pressure of Oxygen) in ambient air is 159 torr \((760\text{mmHg} \times 20.95\% \text{ of O}_2)\) (Fulco and Cymerman, 1987). Exposure to partial pressures of oxygen below this level stimulates physiological changes to sustain oxygen supply to the tissues. On ascent to high altitude, decreases in barometric pressure, decreases partial pressure of oxygen. At 1000m (3280 ft), \( \text{PO}_2 \) is 141torr, and at 4000m (9840 ft), partial pressure is reduced until 110torr (Cheung, 2010). Decreased \( \text{PO}_2 \) in ambient air directly reduces \( \text{P}_{\text{I}}\text{O}_2 \) (Inspired Oxygen Pressure), which results in an interrupted oxygen supply to the body tissues. In turn, the respiratory, cardiovascular and metabolic systems are adjusted to compensate for
low availability of oxygen (Buchheit et al., 2004). These physiological adjustments include an increase in ventilation, alteration in central and peripheral hemodynamics, hematologic changes and metabolic changes (Beidleman, Staab and Glickman, 2005; Young and Reeves, 2002). In addition, the central nervous system is very sensitive to hypoxia so that neuropsychological functioning is altered (Armstrong, 2000).

**Normobaric Hypoxia and Hypobaric Hypoxia**

Hypoxia is the condition in which \( \text{PO}_2 \) is decreased. Hypobaric hypoxia is defined as a reduced barometric pressure (\( \text{Pb} \)) in which ambient air is 20.93% oxygen, or it is the same as sea-level, and therefore the \( \text{Pb} \) \( \text{O}_2 \) varies but the ambient air is always 20.93% oxygen, but oxygen the molecules are farther apart. Normobaric hypoxia is achieved by lowering the \( \text{O}_2 \) content with a fixed \( \text{Pb} \). Both the two conditions result in physiological changes, and, if so, the question is whether these different environmental stressors elicit different physiological responses at the same \( \text{PO}_2 \). Few studies have been completed to answer this very important experimental question.

One study by Tucker et al. (1983) compared normobaric and hypobaric hypoxia, and reported higher minute ventilation (\( \text{VE} \)) in normobaric hypoxia with no significant change in \( \text{SaO}_2 \). However, Loeppky et al. (1997) reported that after 30 min, there was no difference in \( \text{VE} \) between two conditions, but higher \( \text{SaO}_2 \) in normobaric hypoxia than in hypobaric hypoxia. A recent study by Savourey et al. (2003) found that higher breathing frequency and HR and lower minute ventilation (\( \text{VE} \)), tidal volume (\( \text{VT} \)), \( \text{SaO}_2 \) and oxyhemoglobin (\( \text{SPO}_2 \)) in hypobaric hypoxia than in normobaric hypoxia. Even though breathing frequency was higher in hypobaric hypoxia, \( \text{VE} \) was still lower
due to lower VT. In a more recent study, Savourey et al. (2007) reported that lower 
PaCO₂, SaO₂ and higher pH in hypobaric hypoxia when comparing to normobaric 
hypoxia. As a result, hypobaric hypoxia may result in greater dead space ventilation, 
which induces hypocapnia (low CO₂), hypoxemia (low SaO₂) and blood alkalosis 
(higher pH).

**Ventilatory Response**

Acute hypoxia is a potent stimulus for physiological changes. Upon acute 
exposure to hypoxia, the change in ventilation is the primary defense against low oxygen 
availability in ambient air. Due to a decrease in ambient PO₂, pulmonary ventilation 
immediately increases that is due to the severity of hypoxia (Easton et al., 1986). 
Hypoxic conditions decrease PaO₂ (Partial Pressure Oxygen in blood) and consequently 
the oxygen saturation (Van Drop et al., 2007), and it elicits an increase in ventilation, 
which is the result of the hypoxic stimulation of the chemoreceptors on the carotid body 
and aorta (Weil et al., 1970; Fitzgerald and Dehghani, 1982). This mechanism is the 
individual’s initial response to maintain brain and body tissues homeostasis.

Ventilation is altered due to the intensity and duration of hypoxia. An increase in 
ventilation begins immediately, (i.e., within the minutes of exposure to hypoxia 5 to 8 
min) (Young and Reeves, 2002). However, after the initial increase in ventilation a 
decrease may ensue to near normoxic values during the next 10 to 30 min, which is 
called “hypoxic ventilatory depression” (Beidleman, Staab and Glickman, 2005; Pearson 
et al, 2007). This hypoxic ventilatory depression may not result from the response of the 
chemoreceptors since it occurs whether PCO₂ is constant or varied. It is more likely due
to the up-regulation in the central neurotransmitter such as \( \gamma \)-aminobutyric acid (GABA), which is an inhibitory interneuron, and consequently depresses ventilation (Nilsson and Luts, 1993; Kazemi and Hoop, 1991; Smith et al., 2001). In next few hours to days, ventilation increases gradually until the individual becomes acclimated. This phenomenon may be mediated via a progressive increase in carotid body sensitivity and central nervous system acid-base changes (Severinghaus et al., 1963; Bidgard and Foster, 1996; Smith et al., 2001). In normoxic conditions, \( P_AO_2 \) (alveolar \( PO_2 \)) is around 100 torr and venous capillary \( PO_2 \) is around 40 torr (McArdle, Katch and Katch, 2000). This difference in pressure in \( PO_2 \) gradient is critical for gas exchange. However, the difference is lessened in hypoxia, and, in turn, decreases the rate that oxygen diffusion through the membrane of the alveoli (Fulco and Cymerman, 1987). Consequently, it results in low \( PaO_2 \) and \( SaO_2 \) (Roach et al., 2000, Peltonen et al., 2007, Ainslie et al., 2007, Zupet, Princi and Finderle, 2009). Buck et al. (1998) reported that \( PaO_2 \) was 39% lower at 3,000m and 56% lower at 4,500m than normoxic conditions. Buchheit et al. (2004) observed that the difference in \( SaO_2 \) between normoxic and hypoxic conditions was 7.8±0.59% at 11.5% \( O_2 \) (equivalent to 4,800m altitude). In addition, Iwasaki et al. (2007) investigated the effect of gradual decreases (21%, 19%, 17% and 15%, 10 minute for each stage) in ambient air on \( SaO_2 \), and reported that 98±0%, 97±0%, 96±0% and 93±1% of \( SaO_2 \).

**Cardiovascular Response**

In response to a hypoxia condition, cardiac output increases immediately to maintain homeostasis in response to a low oxygen gradient in the blood (Armstrong,
According to Ainslie et al. (2007) cardiac output increased at 4-6 minute after exposure to hypoxia, and returned to baseline by 20 minute. Increases in cardiac output is predominantly due to increase in heart rate because stroke volume remains unchanged (Armstrong, 2000; Wolfel and Levine, 2001; Hainsworth, Drinkhill and Rivera-Chira, 2007). Hypoxia influences the autonomic nervous system, and both sympathetic stimulation and parasympathetic withdrawal are responsible for increased in heart rate (Beidleman, Staab and Glickman, 2005; Buchheit et al., 2004; Hainsworth, Drinkhill and Rivera-Chira, 2007). Heart rate variability is known as a non-invasive indicator of cardiac autonomic nervous system activity, especially vagal activity (Yamamoto, Hoshikawa and Miyashita, 1996), and heart rate variability is reduced in stressful conditions like exercise or hypoxia which increases heart rate (Zupet, Princi and Finderle, 2009). Buchheit et al. (2004) used the time-domain method and the frequency-domain method in their study to analyze heart rate variability, and they observed a significant increase in heart rate and decrease in the root-mean-square of successive normal R-R interval difference and high frequency power, suggesting parasympathetic withdrawal.

Normally, sympathetic stimulation leads to peripheral vasoconstriction, and sympathetic activity increases in acute hypoxia. Then, hypoxic-induced hyperventilation leads to hypocapnia (low PaCO$_2$), subsequently resulting in vasoconstriction (Ainslie et al, 2007). Nonetheless, hypoxic-mediated vasodilation occurs in all vascular beds except the lung (Wolfel and Levine, 2001; Iwasaki et al., 2007). According to
Severinghaus et al. (1966), hypoxic-induced vasodilation may override the vasoconstrictive effect induced by hyperventilation and hypocapnia. Therefore, there may be local vasodilators, which may override vasoconstriction induced by increased sympathetic activity to guarantee oxygen supply. The most convincing candidates are nitric oxide and epinephrine (Halliwill, 2003; Simmons et al., 2007). Maher et al. (2008) compared vascular tones between normoxia and hypoxia with nitrite administration, and observed that the effect of nitrite, which releases nitric oxide, on vasodilation activity is greater in hypoxic condition than in normoxic condition. In short, arterial baroreflex may override sympathetically-mediated vasoconstriction following increased heart rate. However, there are still inadequate information to explain clearly the transient between vasoconstriction and vasodilation following the duration of exposure, magnitude of hypoxia and individual variability.

In addition, sympathetic activity plays a role in maintaining physiologic homeostasis. Although it is limited in effect, some studies suggested that sympathetic activity might prevent forced dilation of the arterioles (Ogoh and Ainslie, 2009a).

**Blood Lactate**

The incomplete breakdown of glucose from glycogen and blood glucose produces the lactate which can be used for gluconeogenesis or production of ATP. However, if the intensity of exercise is great enough and the individual has low aerobic capacity (untrained) then the clearance rate of lactic acid is lower than the production rate. This increase in blood lactate concentration will lead to fatigue due to a decrease in
potassium in muscle cells due to the decrease in pH (Aagaard & Bangsbo, 2006). This is known as the anaerobic threshold and also known as hitting the wall.

As an individual becomes “fit” by increasing their aerobic fitness there will be an increase in the buffering process of lactate from the blood. With increasing exercise intensities the concentrations in lactate and its cotransported hydrogen ions (Hargreaves and Spriet, 2006) will increase but will be buffered by bicarbonate more efficiently than an individual that has a lower aerobic capacity or is untrained. The lack of sufficient buffering of increasing blood lactate in untrained persons can lead to earlier fatigue and termination of the activity due to the decrease in blood pH (Aagaard & Bangsbo, 2006).

**Altitude and Blood Lactate**

As one ascends to altitude blood lactate levels increases at a given workload during submaximal and maximal exercise. However, peak blood lactate concentrations will remain similar to levels seen while exercising at sea level (Lundby & Saltin, 2000; Wilber, 2004). Although muscle and blood lactate concentrations increase with acute exposure to a hypoxic environment the “lactate paradox” describes the phenomenon where the levels decrease with continued exposure to altitude. Nevertheless, studies examining this paradox have been inconsistent and could be intrinsically flawed (Wagner, 2007).

It is important to understand the changes that occur when exposed to hypoxia and how these changes can affect the lactate concentration levels. Kayser (1996) stated that the increase in lactate may be attributed to the changes in muscle metabolism such that pyruvate is produced at a rate greater than the rate it can be reused in the Citric Acid
Cycle. Thus, the pyruvate in excess is then converted to lactate which, in turn, causes an increase in the concentrations (Wagner, 2007). However, with acclimatization to altitude lactate concentration will decrease even when hypoxia levels remain the same or increase. In fact, Lundby’s (2000) data from a study of Danish lowlanders showed a decrease in peak blood lactate after four weeks of acclimatization to 5400 meters, but then decreased to levels similar to those witnessed during acute exposure of the subjects.

The concentration of blood lactate during submaximal exercise during acute hypoxia (first few hours) has been shown to be greater than exercising at similar intensities at sea level. Also, the combination of concentration increases in lactate and hydrogen ion concentrations can lead to a diminished ability for cross-bridging which causes a reduction in anaerobic performance (Wilber, 2004). This should be noted for an individual that will be exposed to altitude for an activity requiring short bursts of activity as those engaged in many sporting events.

**Cerebral Blood Flow**

Cerebral blood flow can be altered by environmental, physical and physiological stressors, and it could cause various clinical illnesses when altered, such as acute mountain sickness (AMS) and high altitude cerebral edema (HACE). Cerebral blood pressure is determined by the balance between the effect of cerebral perfusion pressure and vascular tone (Ogoh and Ainslie, 2009a). In contrast to other organs, cerebral blood flow is relatively constant (Lassen, 1974), and independent from the changes in cerebral perfusion pressure or arterial blood pressure due to dynamic cerebral autoregulation (Iwasaki et al., 2007, Atkins et al., 2010). However, the mechanism for cerebral blood
flow regulation including autonomic nervous system is not solely explained (Secher, 2008).

In response to acute hypoxia, respiratory and cardiovascular systems are immediately altered, and these adjustments may change in response to cerebral blood flow. In the early stage of acute hypoxia, vasodilatory effects, decreases in PaO$_2$ and SaO$_2$, are strong stimuli to increases in cerebral blood flow (Severinghaus, et al., 1966; Cohen et al., 1967; Buck et al., 1998). The traditional theory related to acute hypoxia was that it caused vasodilation, and thereby stimulated chemoreceptors to adjust the autonomic nervous system so that cerebral oxygen consumption was not largely affected by hypoxia. Roach and Hackett (2001) also reported that oxygen supply to the brain is well protected. Buck et al. (1998) studied the effect of acute hypoxia on global cerebral blood flow, and found that global cerebral blood flow increased significantly at 4500m. However, Ainslie and Poulin (2004) found that hypoxia-induced hyperventilation lowers PaCO$_2$, and it, in turn, causes cerebral vasoconstriction so that consequently the change in cerebral blood flow is slight. Another study by Ainslie et al. (2007) found that mean cerebroarterial velocity was maintained even though marked hypocapnia was observed. Therefore, the magnitude of initial change in cerebral blood flow in acute hypoxia may be based on both the magnitude of hypoxia and individual variability such as chemosensitivity (Brugniaux et al., 2007).

Exercise as we know modifies the cardiovascular system, but it is not clear that exercise alters cerebral blood flow. Earlier studies demonstrated that cerebral blood flow is not affected by various conditions due to cerebral autoregulation. The studies by
Globus et al. (1983) and Madsen et al. (1993) found that no significant change in blood flow during physical activity ensued even though significant changes in cardiac output and blood pressure were evidenced. However, recent studies indicated that cerebral artery flow velocity and cerebral blood flow increase during exercise (Thomas et al., 1989; Jorgensen et al., 1992; Ide and Secher, 2000; Secher et al, 2007; Querido and Sheel, 2007). The equivocal findings remain unclear. According to a review by Ogoh and Ainslie (2009a), the varying results between earlier studies and recent studies may be due to different methods to assess cerebral blood flow. While recent studies used TCD (Transcranial Doppler Ultrasound), earlier studies used Kety-Schmit method or 133X (radioisotope), which may have underestimated the response of cerebral response to exercise.

Increase in cerebral blood flow during exercise is attributed to increase in cerebral neuronal activity and metabolism. Cerebral blood flow increases as intensity of exercise increases, but return to baseline even though the relative intensity of exercise rate continues to increase to approximately 60% of VO$_2$max (Ogoh and Ainslie, 2009a). During moderate intensity exercise, PaCO$_2$ does not decrease markedly, and thus cerebral blow flow increases via vasodilation for an increase in energy requirement of the brain. However, further increase of exercise intensity induces decrease in PaCO$_2$, which is a strong stimulator of vasoconstriction (Secher, Seifert, and Van Lieshout, 2007). Therefore, CO$_2$ seems to be an important factor to control cerebral blood flow.

As a result, the vasodilation and the vasoconstrictor effects may be overridden based on changes in CO$_2$ in arterial blood following the intensity of exercise and the
level of the hypoxic condition. During low to moderate exercise, the vasodilatory effect increases cerebral blood flow following an increase in brain metabolism, but if the intensity of exercise increases further, the vasoconstrictor effects will override the vasodilatory effects. This same concept is applied to the hypoxic conditions. In the moderate hypoxic condition, cerebral blood flow increases via vasodilation. However, in the extreme hypoxic condition, this may leads to hypoxic-induced hyperventilation, which augments the effects of the vasoconstrictor effects.

**Cerebral Oxygenation**

While muscles are not affected much by more than a 10% reduction of oxygen, the brain cannot maintain its function when the average oxygenation drops more than 10% (Secher, Seifert and Van Lieshout, 2007). Increase in oxygen consumption by the brain due to exercise results from the competition with the need of oxygenation for skeletal muscles. During exercise, PaO$_2$ and hemoglobin increase to guarantee oxygen supply to the brain. However, maximal exercise decreases PaO$_2$ followed by cerebral deoxygenation. During high intensity exercise, hyperventilation lowers PaCO$_2$, which, in turn, leads to cerebral vasoconstriction. In addition, lowered pH decreases hemoglobin O$_2$ saturation (Powers et al., 1988; Nielsen et al., 1999).

Exercise in hypoxic conditions may further decrease in PaO$_2$ so that cerebral deoxygenation is reduced. Although there are compensatory effects with regard to cerebral blood flow, regional cerebral hypoxia still may ensue. Imray et al. (2005) demonstrated that PaO$_2$ and regional cerebral oxygenation decrease progressively as intensity of exercise and altitude increase. It is supported by Subudhi, Dimmen and...
Roach (2007) who investigated the effects of acute hypoxia on cerebral oxygenation during exercise. They reported that regional cerebral oxygenation and blood volume were not changed during low intensity exercise. However, during high intensity exercise, cerebral oxygenation decreased.

In addition, it does not appear that increases in cerebral blood flow can always maintain adequate cerebral oxygenation. Imray et al. (2003) found that regional cerebral deoxygenation occurred even though cerebral blood flow increased. Peltonen et al. (2007) investigated that cerebral and muscle oxygenation in acute hypoxic ventilatory test, and reported that cerebral deoxygenation, but not muscle, increased during acute hypoxia. However, it was not related to the response of vascular tone and ventilatory chemosensitivity during graded hypoxia. Ainslie et al. (2007) illustrated that mean cerebral arterial velocity was maintained during hypoxic conditions of exercise, but cerebral oxygenation was reduced. As a result, during exercise at high altitude, ventilatory, cardiovascular and cerebrovascular systems are adjusted to maintain oxygen supply to the brain due to increased brain metabolism. Nevertheless, cerebral oxygenation is exacerbated gradually as an exercise intensity and altitude increase oxygen availability decreases.

**Arterial O\textsubscript{2} Saturation and Training Status**

Differences in the physiological responses during exercise of individuals that are highly trained and possess a high aerobic capacity versus those who are sedentary are well known. Individuals who aerobically train regularly improve the oxygen delivery to
the working muscles due to an increase in myoglobin and increase in stroke volume (Nieman, 2007). Therefore, aerobic capacity is increased.

However, research has shown there are no differences between the two groups during exercise in normoxia. Powers et al. (1988) demonstrated that between trained and untrained subjects there was no difference with respect to $\text{SaO}_2$ during submaximal exercise in normoxia. Conversely, at altitude, trained subjects do demonstrate a greater arterial desaturation during maximal exercise in hypoxia (Woorons et al., 2007 and Gore et al., 1996).

Woorons et al., 2007 demonstrated that trained males (trained an average of 10 hours per week) had a greater arterial desaturation during moderate exercise in hypoxia (simulation of 2500 meters) than untrained males. Additionally, the study demonstrated no differences during normoxia between trained and untrained individuals. The differences may be due to the physiological adaptations of the aerobically trained individuals. An increase in cardiac output and reduced red blood cell transit time (Mollard et al., 2007) will allow for increased oxygen delivery to the working muscle. However, this could be the underlying factor in the arterial desaturation in trained males during submaximal exercise in hypoxia.

**Conclusion**

Hypoxia is pathophysiological condition, which results in a low oxygen supply to the human bodily tissues, and causes many physiological alterations. Therefore, it is a salient issue for military personnel as troops, mountain rescue teams and certain athletes who are regularly deployed and involved in physical activities in these environmental
extremes. Research has evaluated the effect of hypobaric hypoxia and exercise for many years. However, the effect of hypoxia and its effect on the human physiological and cognitive responses are equivocal and vary by the environmental extremes, the duration of the stressor, ambient temperature, the individuals’ disease state, as well as fatigue. Therefore, further studies are needed gain a better understanding in this area of inquiry.

Hypoxia and exercise in hypoxia induces oxygen desaturation in arterial blood and cerebral deoxygenation. Even though blood velocity to the brain fluctuates, cerebral deoxygenation decreases gradually, exercise can further exacerbate (Imray et al, 2005; Subudhi, Dimmen and Roach, 2007) the stress on the body. Prefrontal, premotor and motor cortex are part of the regions where deoxygenation may occur, and deoxygenation may be greater in prefrontal than other regions (Subudhi et al, 2009). This phenomenon may elicit cognitive dysfunction. According to the recent clinical investigations with elderly patients, cerebral deoxygenation is significantly associated with cognitive decline (Slater et al, 2009).

The present investigation will build upon and extend the experimental literature and will integrate the effects of hypoxia and aerobic training.
CHAPTER III

METHODOLOGY

Subjects

Twenty college aged (18-22) apparently healthy individuals were recruited to participate in the study via direct contact with the principal investigator. Due to the nature of the trials, the subjects needed to be low altitude residents and not have been exposed to normobaric hypoxia of altitudes above 2500 meters within two months prior to the study. Participants were excluded from the study if they; 1) smoke, 2) possess signs and symptoms or known to have cardiovascular, metabolic, or respiratory disease, 3) experienced syncope, anemia, or fainting while exercising or immediately following exercise. These criteria were determined by a health history questionnaire. Informed consent was obtained from each participant prior to the start of the study. Once the subject was deemed healthy to participate they will underwent a maximal oxygen consumption test to assess fitness. The participants fell into one of the two categories of trained ($\text{VO}_{2\text{max}} \geq 48.2 \text{ ml/kg/min}$) or untrained ($\text{VO}_{2\text{max}} \leq 37.1 \text{ ml/kg/min}$). The classifications were based on the age-related norms within the 20-29 year old age group and represent above the 80th percentile (above average) and the 20th percentile (below average), respectively (Hoffman, 2006). Three participants were included each group.

Research Design

The experimental design that was used for the study was counterbalanced, within trials, and between subjects design. Two subject groups were recruited for the study which included trained ($n = 3$) and untrained ($n = 3$). All subjects took part in two trials
(hypoxia with exercise and normoxia with exercise). Each trial will consisted of a two hour baseline, one hour of exercise, and one hour of recovery. There was also a one week washout period between the two trials for each subject.

During the hypoxia trial, the partial pressure of the inspired oxygen was 91.2 torr (760 mmHg pressure x 12% oxygen) within the altitude simulation chamber. The inspired oxygen during the normoxia trial was 152 torr (760 mmHg pressure x 20% oxygen). The 12% oxygen exposure was similar to that of an altitude of 4300 meters (14,110 feet).

When ascending to 4300 meters, an individual’s maximal aerobic capacity is decreased by 26% from sea-level values (Fulco et al., 1998 and Beidleman et al., 2009). In the hypoxia trial, exercise intensity was 50% of the modified VO$_{2\text{max}}$ which was a 26% decrement of VO$_{2\text{max}}$ from sea-level. During the normoxia trial, the workload was the same as the workload set for the hypoxic trial. Exercise consisted of cycling on a cycle ergometer for one hour. Both of the trials took place at the Exercise Physiology Lab at Kent State University between the hours of 7:00 a.m. and 12:00 a.m.

**Experimental Procedure**

Participants reported to the Exercise Physiology Lab at Kent State in the mornings during the post-absorptive state. The subjects then entered the hypoxic chamber. During the first two hours, the subjects were seated to collect baseline data. Following the rest period, the participants exercised on a cycle ergometer (Excalibur 1300w) at 50% of modified VO$_{2\text{max}}$ for one hour. Following the exercise, the subjects were seated again for a one hour recovery period.
During each four hour trial blood oxygen levels (% O₂ saturation), cerebral O₂, and heart rate were monitored via a pulse-oximeter, Near Infrared Spectroscopy, and a polar heart rate monitor, respectively. Expired air data was collected every 30 minutes as well as five minutes prior to exercise, five minutes after the start of exercise, 15 minutes into exercise, 30 minutes into the exercise, 45 minutes into exercise, 55 minutes into exercise, and five minutes after exercise ended. A Parvo Metabolic Cart was used to analyze expired air. Blood lactate was analyzed at baseline, one hour, five minutes before exercise, five minutes after the start of exercise, 30 minutes into exercise, 55 minutes into exercise, five minutes following the end of exercise, and one hour after exercise ended.

**Instrumentation**

**Hypoxia Chamber**

CAT (Colorado Altitude Training, Louisville, CO) system was used for the simulation of altitude for the study. This system controls altitude setting automatically by sensing oxygen, carbon dioxide, and atmospheric pressure within the chamber. CAT has been applied to various research related to exercise training, aviation, military, and altitude application (Wilber, 2001; Richardson et al., 2008, Kim et al., 2011).

**Near-Infrared Spectroscopy**

Near-Infrared Spectroscopy (NIRS) (Somanetics, Troy, MI) was used noninvasively to monitor hemodynamics and tissue oxygenation (Brazy, 1991). This system has been used to measure cerebral blood flow and oxygenation (Peltonen et al., 2006; Subudhi et al., 2007, Ogoh and Ainslie, 2009, Kim et al., 2011). Also, Henson et
al. (1998) and Tran (1999) validated that NIRS was correlated with oxygen consumption by muscle and cerebral tissue.

**Pulse-Oximeter**

Pulse-Oximeter (Oxi-Go, Roslyn, NY) was used as a noninvasive way to measure oxygen saturation in the arterial blood. Cornolo et al. (2004), Peltonen et al. (2007), Ainslie et al. (2007) and Kim et al. (2011) used the device within their respective studies. Martin et al. (1992) reported that the pulse-oximeter is more accurate than an ear probe and that it is a valid predictor of arterial oxygen saturation during exercise. Gehring (2006), however, showed that the manufacturer’s guidelines for placement of the device should be followed for an accurate measurement.

**Metabolic Measurement System**

Parvo metabolic measurement system (Parvo, Metabolic Cart; Sandy, Utah) was used to analyze and monitor air samples by way of an indirect automated open circuit system to determine oxygen consumption. This system has been commonly used in current research and it provides accurate and reliable data for gas exchange (Crouter et al., 2006; Cooper et al., 2009). The accuracy of the CO₂ and O₂ analyzer is 0.1% (Parvo, Metabolic Cart; Sandy, Utah).

**Cycle Ergometer**

An Excalibur 1300W magnetically braked cycle ergometer (Lode Excalibur Sport, Lode, Groningen, The Netherlands) was used for the cycling exercise.
Heart Rate Monitor

A Polar heart rate monitor (Accurex Plus, Polar Electro, Inc.; Woodbury, NY) was used in the study to monitor heart rate.

Lactate

A Blood Lactate Pro Test Meter (Arkray; Shiga, Japan) was used to analyze blood lactate. A small finger prick was used to draw the blood needed for analysis via a Unistik 3 Extra Lancet (Owen Mumford; United Kingdom). The Lactate Pro has been demonstrated to possess excellent reliability and accuracy compared to traditional laboratory based analyzers (Tanner, Fuller, and Ross, 2010).

Data Analysis

The study included two treatments including normoxia with exercise and hypoxia with exercise. Also, the study consisted of two groups categorized by fitness level (fit and unfit). The data collected was analyzed using the SPSS program and, more specifically the data was analyzed using a two-way repeated measures analysis of variance (ANOVA).
CHAPTER IV
ORIGINAL RESEARCH MANUSCRIPT

Cerebral Blood Flow and Arterial Saturation Between Fit and Unfit Males During Exercise in Hypoxia

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Kent State University – Kent, Ohio

Abstract

Previous research suggests that physical activity may result in lead to decreases in arterial saturation (SaO₂) and cerebral blood flow when exposed to a low oxygen environment between aerobically fit and unfit males. **Purpose:** The purpose of this study was to determine differences in SaO₂, cerebral blood flow, minute ventilation (Vₑ), and blood lactate between fit and unfit young males during exercise in hypoxia compared to normoxia. **Methods:** Apparently healthy college age males took part in two trials consisting of normobaric normoxia and normobaric hypoxia (12% oxygen). Fit (n = 3; VO₂max = 51.5 ml • kg⁻¹ • min⁻¹ ± 3.1) and Unfit (n = 3; VO₂max = 34.4 ml • kg⁻¹ • min⁻¹ ± 5.6) cycled at 50% of their altitude adjusted VO₂max (-26% of normoxia VO₂max) for one hour after a two-hour baseline. **Results:** SaO₂, cerebral blood flow, and RER were significantly decreased during hypoxia in all subjects (P < 0.05), but did not differ between groups. An interaction effect showed that Fit subjects had a higher SaO₂ during exercise in hypoxia (P < 0.05). Vₑ and lactate was greater during hypoxia (P < 0.05). The Fit group demonstrated a higher Vₑ during exercise in hypoxia (P < 0.05). No
differences in blood lactate were found between the two groups. **Conclusion:** The data suggests that when exposed to hypoxia aerobically unfit males may demonstrate decrements in oxygen utilization which may lead to decreases in physical activity and/or performance.

**Introduction**

Oxygen is the most important element used by the human body for energy utilization during an aerobic activity. The lack of oxygen (hypoxia) can occur from diseases of the airways (i.e. chronic obstructive disease and sleep apnea) or from a high altitude environment. At altitude, the partial pressure of oxygen is decreased; therefore, the same volume of air at altitude contains less oxygen than at a lower altitude. Boyle’s law states that volume is inversely proportional to pressure. The decrease in barometric pressure as well as the partial pressure of oxygen will hinder gas exchange. The human body attempts to compensate for the limited availability of oxygen via cardiovascular (increased heart rate and cardiac output) and pulmonary (increased rate and volume of breathing) responses. These cardiopulmonary responses are an attempt to combat the decreased ambient oxygen content in order to provide oxygen to the active tissues. These responses continue until the individual becomes acclimatized due to peripheral chemoreceptor responses to hypoxia (Bartsch and Saltin, 2008).

Research suggests that physical activity may result in further decreases in arterial oxygenation. It has been shown that maximal cycling at high altitude will further decrease arterial saturation (SaO₂) due to the decrement in the alveolar pressure of oxygen (Gore et al., 1996). While cycling in normobaric hypoxia following two hours
of baseline, Glickman et al. (2010) also demonstrated that cerebral oxygenation was significantly decreased in middle-aged males during submaximal cycling exercise when compared to resting in normobaric hypoxia. Exercise may also cause an increase in cerebral blood flow that will continue to rise with the intensity of exercise. However, even though increasing exercise intensity may further increase cerebral blood flow, brain blood flow may progressively decrease to baseline values once exercise reaches 60% of maximal aerobic capacity (VO$_{2\text{max}}$) (Ogoh and Ainslie, 2009).

Physical fitness (i.e., aerobic training) greatly contributes to an individual’s response to a given environmental stressor they are not acclimated to. Hypoxic conditions have been shown to cause the body to react differently between trained and untrained individuals. Mollard et al. (2007) demonstrated that SaO$_2$ was significantly lower in trained male subjects compared to untrained subjects. In a similar study, Woorons et al. (2007) also demonstrated a significant difference in SaO$_2$ between trained and untrained college-aged males while cycling in normoxia and hypoxia. The data demonstrated that the SaO$_2$ was significantly lower in the trained group compared to the untrained group. It has been suggested that the causes of this decrement may be due to an increased response of trained individuals to hypoxia (i.e. increased ventilation) (Mollard et al., 2007; Woorons et al., 2007). Increased cardiac output (Q) during exercise as a result training and increased physical fitness (aerobic training) may also play a role in the decrease in SaO$_2$ (Bartsch and Saltin, 2008). The increased Q as well as an increased size and number of muscular mitochondria of the aerobically fit individuals may lead to more blood reaching the working tissue and thus the delivery
oxygen more rapidly than aerobically unfit individuals. In response, SaO₂ and cerebral blood flow in fit individuals may be decreased.

The purpose of the present study was to evaluate the physiological differences (i.e. cerebral blood flow, arterial saturation, respiratory responses, and blood lactate) between aerobically fit and unfit college age males in response to exercise in normobaric hypoxia versus normobaric normoxia.

Methods

Subjects

Six college age males not acclimatized to altitude volunteered for the study. All subjects were non-smokers, apparently healthy with no history of cardiovascular or respiratory conditions. The subjects were categorized into two groups based on VO₂max: aerobically fit (FT, n = 3) and aerobically unfit (UF, n = 3). The fit individuals tested at a VO₂max of ≥48.2 ml • kg⁻¹ • min⁻¹ while the unfit individuals tested at VO₂max of ≤37.1 ml • kg⁻¹ • min⁻¹. The classifications were based on age-related norms within the 20-29 year old age group and represent the 80th percentile and the 20th percentile (Hoofman, 2006). Informed consent was obtained from each subject as well as a health history questionnaire and a prescreening evaluation prior to participating in the study.
Table 1. *Subject Characteristics*

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Subjects (n = 6)</th>
<th>FT (n = 3)</th>
<th>UF (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22.2 ± 1.6</td>
<td>23.0 ± 1.7</td>
<td>21.3 ± 1.2</td>
</tr>
<tr>
<td>Height (cm)</td>
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<td>176.3 ± 7.6</td>
<td>174.3 ± 4.0</td>
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<tr>
<td>Weight (kg)</td>
<td>91.4 ± 25.3</td>
<td>72.7 ± 4.3</td>
<td>110.0 ± 23.1</td>
</tr>
<tr>
<td>VO$_{2\text{max}}$ (ml/kg/min)</td>
<td>43.0 ± 10.2</td>
<td>51.5 ± 3.1</td>
<td>34.4 ± 5.6*</td>
</tr>
</tbody>
</table>

**Maximal Aerobic Capacity**

The subjects reported to the Exercise Physiology Lab at Kent State University on the first visit to determine VO$_{2\text{max}}$. The subjects cycled on an Excalibur 1300W magnetically braked cycle ergometer (Lode Excalibur Sport, Lode, Groningen, The Netherlands) and oxygen consumption was determined using a Parvo metabolic measurement system (Parvo, Metabolic Cart Sandy, Utah). The metabolic cart used is commonly used in current research and it has shown to provide accurate and reliable data for gas exchange (Cooper et al., 2009). All equipment was calibrated to ambient temperature, barometric pressure and relative humidity. Once VO$_{2\text{max}}$ was determined the subject were placed in the fit group or unfit group.

**Blood Flow and Oxygenation**

Cerebral blood flow was analyzed using Near-Infrared Spectroscopy (NIRS) (Somanetics, Troy, MI). This system has been used to measure blood flow and oxygenation (Peltonen et al., 2006; Subudhi et al., 2007; Ogoh and Ainslie, 2009; Kim et al., 2011). NIRS has also been correlated with oxygen consumption by muscle and cerebral tissues (Hensen et al., 1998; Tran, 1999, Neary et al., 2002). Arterial oxygen
saturation ($\text{SaO}_2$) was determined via a Pulse-Oximeter (Oxi-Go, Roslyn, NY). Martin (1992) reported that the Pulse-Oximeter is more accurate than an ear probe and is a valid predictor of arterial saturation during exercise. Recent studies have used this device to accurately measure $\text{SaO}_2$ (Cornolo et al., 2004; Peltonen et al., 2007; Ainslie et al., 2007; Kim et al., 2011). Sensors were placed on the forehead of each subject. One sensor was on the right side and one on the left. The sensors continuously recorded cerebral blood flow during the four-hour trials. Data was analyzed by determining the percent changes in blood flow from baseline (0 minutes).

**Blood Lactate (BL) and Glucose (BG)**

Finger sticks using Unistik 3 Extra Lancet (Owen Mumford, United Kingdom) were performed to analyze blood for lactate and glucose. A Blood Lactate Pro Test Meter (Arkray; Shiga, Japan) was used to analyze lactate and has been demonstrated to provide excellent reliability and accuracy (Tanner et al., 2010). Blood glucose was determined via Accu Chek Compact Plus Meter and test strips (Roche Diagnostics; Mannheim, Germany).

**Hypoxic and Normoxic Trials**

The second and third visits to the lab (separated by at least 7 days) consisted of a normobaric hypoxic trial (21.5% ambient oxygen) and a normobaric normoxic trial (12% ambient oxygen). The order of the trials was counterbalanced. During each of these trials the subject’s baseline data consisting of RER, minute ventilation (VE), $\text{SaO}_2$,
cerebral blood flow, and blood lactate was analyzed before entering a hypoxic chamber (Colorado Altitude Training, Louisville, CO). This chamber (CAT) controls the altitude setting automatically by sensing oxygen, carbon dioxide, and atmospheric pressure within the chamber. CAT has been applied to various research related to exercise training, aviation, military and altitude application (Wilbur, 2001; Richardson et al., 2008; Kim et al., 2011). The subjects entered the chamber whereby the ambient oxygen simulated 4300 meters (12% O₂) and remained at rest for two hours prior to exercise.

Five minutes prior to the start of a 1-hour submaximal exercise bout and five minutes after the start of exercise all of the aforementioned data were analyzed. The subjects also rested for a 1-hour recovery period after exercise whereby data was collected at the end of the recovery. Each subject’s VO₂max was modified since maximal aerobic capacity is decreased by 26% from sea-level values (Fulco et al., 1998; Beidleman et al., 2009). The subjects exercised at 50% of their modified VO₂max during the 1-hour cycling exercise.

Figure 1. Timeline of Data of Baseline, Pre-Exercise, During Exercise, Post Exercise, 1 hour Post-Exercise.
Results

Arterial Saturation

An ANOVA showed no significant difference between groups for SaO$_2$ ($P = 0.289$) throughout hypoxia. However, there was a significant difference between conditions ($P < 0.001$) as well as time ($P < 0.001$) showing a decreased arterial saturation during hypoxia and throughout the exercise bout in both groups. The results also showed that the Unfit group did have a lower SaO$_2$ as exercise progressed during hypoxia, but not during normoxia, but the difference was not significant between groups.

Figure 2. SaO$_2$ during hypoxia between groups
Cerebral Blood Flow (NIRS)

NIRS data was based on a percentage of change compared to baseline levels. A repeated-measures ANOVA revealed no significant difference between groups in the NIRS left (P = 0.601) and the NIRS right (P = 0.373). While there were no differences between groups, the analysis showed a significant difference between hypoxic and normoxic conditions in NIRS left (P = 0.001) and NIRS right (P < 0.001). A main effect for time was seen in both NIRS left and right (P < 0.001 and P = 0.01, respectively).

The data suggests that although the groups did not differ in cerebral blood flow as exercise began, blood flow to the brain was either increased (during normoxia) compared to baseline or decreased (during hypoxia) compared to baseline.

However, analysis showed that cerebral blood flow was significantly different five minutes post-exercise in hypoxia (P = 0.007) between the two groups. However, no other time points were statistically significant. This shows that brain blood flow was higher immediately after exercise in the Unfit group compared to the Fit group.
Figure 3. NIRS right during hypoxia between groups

Figure 4. NIRS Left during hypoxia between groups
Minute Ventilation ($V_E$) and RER

$V_E$ was significantly different in between conditions ($P = 0.002$) with fit group demonstrating a greater $V_E$ during the exercise in hypoxia ($P = 0.05$). This result suggests that the fit individuals would be utilizing more $O_2$ during the exercise stress for the working tissues as well as compensating for the decreased $O_2$ concentration during hypoxia. Although both groups showed increased $V_E$ during hypoxia versus normoxia, the fit group showed a higher volume in each condition during the exercise bout, but only statistically significant during the exercise bout in hypoxia.

The data also showed a trend towards significance in RER ($P = 0.069$) whereby the fit group had a lower RER during both conditions. Additionally, during much of hypoxia trial the fit group showed a lower RER even throughout the exercise bout. A main effect for time ($P < 0.01$) and a trial by time interaction ($P < 0.01$) demonstrated that the subjects’ RER was decreased during exercise in hypoxia compared to exercise during normoxia. Toward the end of exercise in hypoxia (EX2) $V_E$ in the fit group was significantly greater than that of the unfit group ($P = 0.005$) (Figure 6).
Figures 5. $V_E$ during Normoxia between groups

Figures 6. $V_E$ during Hypoxia between groups
Figures 7. RER during normoxia between groups

Figures 8. RER during hypoxia between groups
Blood Lactate
There was no significance found between groups (P = 0.703) in blood lactate response. However, a within-subjects analysis revealed BL was significantly increased during the hypoxic conditions (Mean = 6.3 ± 0.6 mmol/L) compared to the normoxic conditions (Mean = 4.5 ± 0.9 mmol/L) in all subjects (P = 0.018) throughout the exercise.

*Figure 9. Blood lactate between normoxia and hypoxia trials*

Discussion
This study was designed to evaluate the physiological responses to exercise in hypoxia between aerobically fit and unfit individuals utilizing NIRS during normobaric hypoxia. Interestingly, much of the data that proved to be statistically significant is representative
of the differences between fit and unfit populations when individuals are exposed to normobaric hypoxia. Compared to the results of previous studies (Mollard et al., 2007; Woorons et al., 2001) the present study demonstrated a greater arterial saturation in the fit group compared to the unfit group during submaximal exercise in hypoxia. Other studies have demonstrated lower SaO$_2$ in the fit group during maximal exercise (Gore et al., 1996; Woorons et al., 2005). However, the present study did not elicit the same responses in SaO$_2$ while using a modified (-26% of VO$_{2\text{max}}$) for the exercise intensity. One reason for the disparity of these results in the current study between fit and unfit individuals could be that the exercise intensity or duration may not have been great enough to elicit a greater change in SaO$_2$. The previous studies demonstrated differences at higher exercise intensities. Therefore, it can be suggested that low to moderate exercise intensities during hypoxia did not elicit differences between aerobically fit and unfit males in this environmental extreme. However, the current results demonstrating a decreased SaO$_2$ during exercise in hypoxia compared to normoxia are similar to previous studies (Glickman et al., 2010; Gore et al., 1996).

The responses in the present study with respect to cerebral blood flow via NIRS demonstrated that both the fit and unfit groups demonstrated a similar response. Within 5 minutes following the cessation of exercise in the unfit group during hypoxia there was an abrupt increase in cerebral blood flow from -26% below baseline to -7% below baseline. Although this response returned to pre-exercise values during recovery, the response was significantly higher than the fit group. This may suggest that when an individual is aerobically more fit blood was shunting away from the working tissues and
may represent a more efficient recovery response by utilizing the \( \text{O}_2 \) that is needed for replenishing glycogen, \( \text{H}^+ \) clearance, and/or a greater response for oxidative stress within the working skeletal muscles. Alternatively, the lower NIRS in the fit group immediately after exercise compared to the unfit group also demonstrated a symptomatic response that was anecdotally noted. Since we hypothesize that blood flow was most probably being diverted to the active skeletal muscle and away from the brain, two of the three volunteers also reported nausea. Although the data does not demonstrate this as being statistically significant between the groups there is a noted difference of how the individuals experience the exercise during normobaric hypoxia.

Due to the lack of significance in cerebral blood flow between groups during hypoxia this may also reveal that the exercise intensity or duration was not great enough to elicit a significant difference. Therefore, as with arterial saturation, cerebral blood flow during low to moderate exercise intensities in hypoxia are not different between aerobically fit and unfit males. The lack of statistical difference may be attributed to the low sample size used in the present investigation and the subsequent low observed power with respect to the left NIRS sensor (0.174), the left side NIRS sensor (0.050), and SaO2 (0.210).

The increase in \( V_{E} \) and SaO2 in the fit group compared to the unfit group during hypoxia may also demonstrate that the fit subjects physiologically are more adapted to endurance exercise. Previous studies that have demonstrated a decrease in SaO2 during hypoxia may have elicited a similar response at a higher intensity of exercise (Woorons et al., 2007) than the present investigation. The response in arterial saturation may
suggest that these subjects respond differently and this response could have occurred due to hypoxemia caused by a combination of an increased exercise stress combined with a low oxygen environment. This may lead to a decrease in SaO$_2$ due to the increased extraction of oxygen coupled with the inability to keep up with oxygen demand to the working tissues. Similar responses are seen in highly trained endurance athletes (exercise-induced hypoxemia). This phenomenon is usually coupled with a significant increase in heart rate, which can lead to decreased pulmonary diffusion. However, the current study showed no significant differences in heart rate between the groups but was significantly higher for both groups during hypoxia (P = 0.066). This suggests that a trend towards hypoxemia, however, the SaO$_2$ and NIRS data did not physiologically support this theory. The data did demonstrate that cardiovascular responses are greater when exposed to hypoxia. Therefore, the lack of highly trained or elite individuals in the present study may not have been great enough to elicit this response. Also, the exercise stressor used in the present study may not have been intense enough to elicit the decreased arterial saturation in aerobically fit group such as Woorons (2006) demonstrated.

Even though respiratory exchange ratio (RER) was not significantly different between the groups and between conditions Figures 6a and 6b depict the trend that the fit group had a lower RER during normoxia but elicited an RER similar to the unfit group during hypoxia. Interestingly, this elucidates that the unfit group demonstrated a glycogen sparing effect as exercise progresses during hypoxia. This may suggest that, both groups seemed to steadily decrease RER during hypoxia compared to the normoxic
condition. This is in contrast to the concept that the lack of oxygen may require the body to rely more on anaerobic energy systems. However, one theory to explain why the unfit group had a lower RER during hypoxia may be that the stress of the exercise combined with the lack of oxygen within the ambient air may lead to an increase in oxygen extraction. The increase in stress can lead to increased hydrogen ions (H\textsuperscript{+}) concentration causing a right shift in the oxyhemoglobin dissociation curve resulting in a greater extraction of oxygen. Therefore, the subjects will be utilizing a greater percentage of the oxygen inhaled. Thus there may be no actual glycogen sparing effect. The response could simply be the result of increasing glycogen and glucose utilization by the unfit individuals.

The responses seen in all subjects show that a “lactate paradox” did not ensue. During submaximal exercise in acute hypoxia blood lactate has been shown to increase over normoxia levels at the same exercise intensity. However, during prolonged exposure to hypoxia blood lactate levels will tend to be similar at a given exercise intensity compared to normoxia (Wagner, 2007). However, the present study did not elicit this response with respect to blood lactate. This suggests that the exposure to hypoxia was not long enough and that the subjects’ blood lactate responses were similar to that of previous studies. A possible explanation may be that in the previous studies with respect to the blood lactate paradox, during hypoxia, the that subjects were acclimatized to the altitude in which the exercise bout took ensued (Lundby, 2000). The current study’s subjects were not acclimatized to the simulated altitude and this could be the limiting factor in eliciting a lactate paradox response.
One additional observation should be made with regard to the differences between the groups in the present study. During the study the subjects were asked how they felt overall throughout the exercise bout. Despite the lack of traditional data two of the three fit subjects said they felt nauseated towards the end of exercise during hypoxia until about 10 to 15 minutes after the exercise bout was terminated. However, the unfit subjects stated they felt as they would during any exercise bout. Comparing the physiological data to this undocumented anecdotal data the “nausea” experienced by the fit group during exercise in hypoxia, but not the unfit group, cannot be explained by the present data. Cerebral blood flow was not significantly different between the groups except at the end of exercise. However, percent change from baseline was only significantly different five minutes after exercise in hypoxia and only in the right sensor of the NIRS. This demonstrated that the unfit group significantly increased their cerebral blood flow immediately after exercise. This could have led to the fit subjects having the feeling of nausea while the unfit subjects demonstrated an increased blood flow to the brain limiting the effects of low oxygen supply to the brain. This may suggest that the unfit individuals were shunting more blood away from the working muscles. Kim (2011) demonstrated an increase in cognitive function after exercise in hypoxia. Therefore, one direction for future studies would be to examine differences among fit and unfit individuals with regards to acute mountain sickness and cognitive function post exercise and during exercise. One theory based on the present study is that the unfit individuals may have elicited increased cognitive performance post exercise due to the significant increase in cerebral blood flow. However, since the cerebral blood
between the fit and unfit individuals were similar within 30 minutes post-exercise differences with regards to cognitive function may be reduced.

In summary, the current study demonstrated that during hypoxia aerobically fit individuals elicited a greater $V_E$ and $\text{SaO}_2$ during a 50% of an altitude modified submaximal exercise. Both groups demonstrated differences between normoxia and hypoxia with respect to: cerebral blood flow, $V_E$, $\text{SaO}_2$, and blood lactate. Further research is needed to determine if greater exercise intensity or duration can lead to a greater response or perhaps cause an exercise-induced hypoxemia during hypoxia, which would cause decrease in the cerebral blood flow and arterial saturation.

The use of NIRS to measure cerebral blood flow and use of a simulated altitude chamber (CAT) has demonstrated to be a viable means of determining physiological responses to a low oxygen environment when traveling to such altitudes is unreasonable due to geographical location. Future research can also look at psychological factors between aerobically fit and unfit individuals and if there is a correlation between physiological and psychological responses during exercise in a hypoxic environment among aerobically fit and unfit individuals by utilizing NIRS and in normobaric hypoxia.
APPENDIXES
APPENDIX A

WRITTEN INFORMED CONSENT
APPENDIX A

WRITTEN INFORMED CONSENT

Informed Consent to Participate in a Research Study

Study Title: The effects of aerobic fitness between apparently healthy aerobically fit and unfit college-aged males during and following exercise in normobaric hypoxia and normoxia.

Principal Investigator: Matthew Vern Bliss, M.A. (Ph.D Candidate in Exercise Physiology)

You are being invited to participate in a research study. This consent form will provide you with information on the research project, what you will need to do, and the associated risks and benefits of the research. Your participation is voluntary. Please read this form carefully. It is important that you ask questions and fully understand the research in order to make an informed decision. You will receive a copy of this document to take with you.

Purpose

Previous studies have looked at differences among trained and untrained individuals exercising in hypoxia (low oxygen environments/high altitude). Others have suggested that there are differences between these two groups (i.e., fit and unfit) in how the body responds to the low oxygen. However, the differences in blood flow to the brain and the amount of oxygen in the blood during one hour of cycling in hypoxia between the trained and untrained college-aged males has been not been revealed. The purpose of the present investigation is to look at the effects of aerobic fitness on cerebral blood flow, heart rate, blood pressure, leg pain, and rating of perceived exertion (RPE) between apparently healthy trained and untrained college-aged males prior to, during, and following exercise in hypoxia.

Procedures

To determine if you qualify for the study, you will be prescreened to insure you are physically able to participate in the study. To qualify for participation in this study you should be a non-smoker, have no signs and symptoms of cardiovascular and respiratory diseases, and/or have no a history of nausea, vomiting, or fainting during or immediately following exercise. Recent or current use of weight loss supplements and other weight loss drugs will also disqualify you from the study.

After you are prescreened and you are physically able to participate, you will be asked to come to the lab for three sessions.
Day 1: Health History Questionnaire, Consent Form (this form), Study Overview (detailed description), VO2max test
Day 2: 4 hour in the chamber with one hour of cycling exercise (hypoxia or normoxia)
Day 3: 4 hour trial with one hour of cycling exercise (hypoxia or normoxia)

The trials must take part at least one week between each other.
Both of the times you are exposed to low oxygen will take place in an altitude simulation chamber which will cause the oxygen amount to be as if you were at 14,000 feet. The oxygen at this altitude will be at a lower amount than here at Kent. However, during one of the trials the air will contain the amount of oxygen as here at Kent. Each trial will last for 4 hours. This will include 2 hours of resting in a chair, 1 hour of cycling exercise on a stationary bike, and 1 hour sitting in a chair which will be a recovery time.

The cycling exercise will last 1 hour and the intensity of the exercise will depend on your personal aerobic fitness. We will determine this by having you participate in a VO2max test (on your first visit to the lab) to measure your maximal aerobic capacity. This test will determine how much oxygen your body can use while you exercise. From this test we can see how hard you will work during the exercise on the bike.

Benefits
The potential benefits of participating in this study may include ability to have data on your aerobic fitness and how your body reacts physiologically to altitude. Both you and society in general will also be able to learn how training status can affect the human body, such as blood flow to the brain, while exposed to a hypoxic environment

Risks and Discomforts
The potential risks involved in participating in this study include nausea, vomiting, light-headedness, or fainting. These all reflect what can occur when exposed to a low oxygen environment.

During the study you may experience light headedness, vomiting, fainting, and leg pain associated with the cycling exercise. If these problems occur we will monitor your symptoms and if they remain the trial will be ended and you will be seated while in normal oxygen (Kent oxygen levels) until your symptoms subside. If they continue to worsen emergency services may be called or you will be taken to the Kent State Health Center for further evaluation. Also, you have the option to withdraw from the study at any point in time if you feel any of these symptoms or you simply do not want to continue and you will be paid for the trials completed.

Medical treatment by the University Health Center is provided only to currently registered students. Please be advised that for all other injuries, emergency services will be called for those occurring on the Kent State University campus. You or your medical
insurance will be billed for this service. No other medical treatment or financial compensation for injury from participation in this research project is available.

**Privacy and Confidentiality**

Your study related information will be kept confidential within the limits of the law. Any identifying information will be kept in a secure location and only the researchers will have access to the data. Research participants will not be identified in any publication or presentation of research results; only aggregate data will be used.

If you agree to participate in this research project, health information that may identify you will be collected. We will collect information from your medical record (from the Health History Questionnaire) including hospitalization, surgeries, medications, allergies, diagnosis of medical diseases/symptoms, family health history, and drug use. We will only collect information that is needed for the research and described in this consent form. By signing this consent form, you are authorizing the study investigators to access your medical record and health information as described in the consent document. This information is standard protocol for participating in research studies involving exercise to ensure you are physically healthy enough to participate in the exercise.

**Compensation**

By participating in the study you will be paid a monetary value of $150 for the completion of the study ($75 per trial). No compensation will be given for the completion of the aerobic fitness test only. If you withdrawal from the study due to medical reasons and/or symptoms mentioned above you will be paid for the trials completed and/or the trial you withdrew from.

**Voluntary Participation**

Taking part in this research study is entirely up to you. You may choose not to participate or you may discontinue your participation at any time without penalty or loss of benefits to which you are otherwise entitled. You will be informed of any new, relevant information that may affect your health, welfare, or willingness to continue your study participation.

**Contact Information**

If you have any questions or concerns about this research, you may contact Matthew V. Bliss at 814-229-7707 or Dr. Ellen Glickman at 216-201-2332. This project has been approved by the Kent State University Institutional Review Board. If you have any questions about your rights as a research participant or complaints about the research, you may call the IRB at 330-672-2704.
Consent Statement and Signature
I have read this consent form and have had the opportunity to have my questions answered to my satisfaction. I voluntarily agree to participate in this study. I understand that a copy of this consent will be provided to me for future reference.

________________________________
Participant Signature

_____________________
Date
APPENDIX B

HEALTH HISTORY QUESTIONNAIRE
APPENDIX B

HEALTH HISTORY QUESTIONNAIRE

KENT STATE UNIVERSITY
APPLIED PHYSIOLOGY RESEARCH LAB

HEALTH HISTORY
Thank you for volunteering to be a participant for a study to be conducted in the Applied Physiology Research Laboratory. Some of the tests used in our experiments require that you perform very strenuous exercise, while other times may be under difficult environmental conditions. Consequently, it is important that we have an accurate assessment of your past and present health status to assure that you have no medical conditions that would make the tests especially dangerous for you. Please complete the health history as accurately as you can.

THIS MEDICAL HISTORY IS CONFIDENTIAL AND WILL BE SEEN ONLY BE THE INVESTIGATORS AND KENT STATE UNIVERSITY HEALTH CENTER PERSONNEL

Name__________________________________________ Date___/___/___

Date of Birth___/___/___ Present Age____yrs

Ethnic Group:  ____White ____ African American
___ Hispanic
___ Asian
___ Pacific Islands
___ American Indian
___ Other__________

HOSPITALIZATIONS AND SURGERIES
If you have ever been hospitalized for an illness or operation, please complete the chart below. Do not include normal pregnancies, childhood tonsillectomy, or broken bones.

YEAR________
OPERATIONS OR ILLNESS
___________________________________________________________________________

YEAR________
OPERATIONS OR ILLNESS
___________________________________________________________________________

YEAR________
OPERATIONS OR ILLNESS
___________________________________________________________________________

Are you under long-term treatment for a protracted disease, even if presently not taking medication?  [ ] Yes  [ ] No
If Yes, explain:__________________________________________________________________________________________________________
___________________________________

MEDICATIONS
Please list all medications that you have taken within the past 8 weeks: (Include prescriptions, vitamins, over-the-counter drugs, nasal sprays, aspirins, birth control pills, etc.)
Check this box [     ] if you have not taken any medication.

MEDICATION________________
REASON FOR TAKING THIS
___________________________________________________________________________________________________________________
___________________
MEDICATION________________
REASON FOR TAKING THIS
___________________________________________________________________________________________________________________
_____________________________
MEDICATION________________
REASON FOR TAKING THIS
___________________________________________________________________________________________________________________
_____________________________

ALLERGIES
Please list all allergies you have (include pollen, drugs, alcohol, food, animals, etc.)
Check this box [     ] if you have no allergies.

1.______________________________________________________________________
2.______________________________________________________________________
3.______________________________________________________________________
4.______________________________________________________________________

When was the last time you were “sick”? (e.g. common cold, flu, fever, etc.)
______________________________________________________________________

PROBLEMS AND SYMPTOMS
Place an X in the box next to any of the following problems or symptoms that you have had:

General

[   ]   Mononucleosis
      If yes, when____________________________________________
[   ]   Excessive fatigue
[   ]   Recent weight loss while not on a diet
[   ]   Recent weight gain
[   ]   Thyroid disease
[   ]   Fever, chills, night sweats
[   ]   Diabetes
[   ]   Arthritis
[   ]   Sickle Cell Anemia
[   ]   Heat exhaustion or heat stroke
[   ]   Recent sunburn
PROBLEMS AND SYMPTOMS, continued

Heart and Lungs

[ ] Abnormal chest x-ray
[ ] Pain in chest (persistent and/or exercise related)
[ ] Heart attack
[ ] Coronary artery disease
[ ] High blood pressure
[ ] Rheumatic fever
[ ] Peripheral vascular disease
[ ] Blood clots, inflammation of veins (thrombophlebitis)
[ ] Asthma, emphysema, bronchitis
[ ] Shortness of breath
  [ ] At rest
  [ ] On mild exertion
[ ] Discomfort in chest on exertion
[ ] Palpitation of the heart; skipped or extra beats
[ ] Heart murmur, click
[ ] Other heart trouble
[ ] Lightheadedness or fainting
[ ] Pain in legs when walking
[ ] Swelling of the ankles
[ ] Need to sleep in an elevated position with several pillows

G-U SYSTEM

[ ] Get up at night to urinate frequently
[ ] Frequent thirst
[ ] History of kidney stones, kidney disease

G.I. TRACT

[ ] Eating disorder (e.g. anorexia, bulimia)
[ ] Yellow jaundice
  If yes, when__________________________
[ ] Hepatitis
  If yes, when__________________________
[ ] Poor appetite
[ ] Frequent indigestion or heartburn
[ ] Tarry (black) stool
[ ] Frequent nausea or vomiting
[ ] Intolerance of fatty foods
[ ] Changes in bowel habits
[ ] Persistent constipation
[ ] Frequent diarrhea
[ ] Rectal bleeding
[ ] Unusually foul smelling or floating stools
[ ] Pancreatitis
Nervous System

[ ] Alcohol problem
[ ] Alcohol use
  If yes, how many drinks ingested per week? ________________
[ ] Frequent or severe headaches
[ ] Stroke
[ ] Attacks of staggering, loss of balance, dizziness
[ ] Persistent or recurrent numbness or tingling of hands or feet
[ ] Episode of difficulty in talking
[ ] Prolonged periods of feeling depressed or "blue"
[ ] Difficulty in concentrating
[ ] Suicidal thoughts
[ ] Have had psychiatric help

Explain any items checked (when, severity, treatment)

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Have you ever passed out during or after exertion? YES NO
Do you have a family history of coronary artery disease?
  If yes, Who? (Grandparents, parents, siblings, uncles, and aunts)

Are there any other reasons not mentioned above that you feel you should not participate in this research study? YES NO

Do you currently smoke cigarettes? YES NO
Do you currently use any smokeless tobacco products? YES NO
APPENDIX C

PRE-SCREENING QUESTIONNAIRE
APPENDIX C

PRE-SCREENING QUESTIONNAIRE

AHA/ACSM Health/Fitness Facility Pre-participation Screening Questionnaire

Assess your health status by checking all true statements:

**History:** You have had:

__________ A heart attack
__________ Heart surgery
__________ Cardiac catheterization
__________ Angioplasty or stent
__________ Pacemaker/implantable cardiac defibrillator
__________ Rhythm disturbance
__________ Heart valve disease
__________ Heart failure
__________ Heart transplantation
__________ Congenital heart disease

**Symptoms:**

__________ You experience chest discomfort with exertion.
__________ You experience unreasonable breathlessness
__________ You experience dizziness, fainting, or blackouts
__________ You take heart medications
__________ Other health issues
__________ You have diabetes
__________ You have asthma or other lung disease
__________ You have burning or cramping sensation in your legs when walking short distances.
__________ You have musculoskeletal problems that limit your physical activity.
__________ You have concerns about the safety of exercise
__________ You take prescription medication(s).
__________ You are pregnant.

**Cardiovascular risk factors:**

__________ You are a man older than 45 years.
__________ You are a woman older than 55 years, have had a hysterectomy, or are postmenopausal
__________ You smoke, or quit smoking within the previous 6 months.
__________ Your blood pressure is greater than 140/90 mm Hg (Last date checked:_______)
__________ You do not know your blood pressure.
__________ You take blood pressure medication.
__________ Your blood cholesterol level is greater than 200 mg/dl (Last date checked:_______)
__________ You do not know your cholesterol level.
You have a close blood relative who had a heart attack or heart surgery before age 55 (father or brother) or age 65 (mother or sister).

You are physically inactive (i.e., you get <30 minutes of physical activity on at least 3 days per week).

You are greater than 20 pounds overweight.
APPENDIX D

RATING OF PERCEIVED EXERTION SCALE
**APPENDIX D**

**RATING OF PERCEIVED EXERTION SCALE**

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<tr>
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REFERENCES


