THE EFFECTS OF ACUTE EXERCISE ON COGNITIVE PERFORMANCE
IN HYPOXIC CONDITIONS

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THE EFFECTS OF ACUTE EXERCISE ON COGNITIVE PERFORMANCE IN HYPOXIC CONDITION (101 pp.)

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INTRODUCTION: Exposure to high altitude or hypoxia may elicit negative cognitive performance and mood state in many individuals. This may place the individuals at undue risk. Moderate intensity exercise may improve psychological and mood state at normoxia but little is known about its effect in hypoxia. PURPOSE: The purpose of this study was to quantify the effects of two exercise intensities on cognitive performance and mood state in normobaric hypoxia. METHOD: 19 young, healthy men completed the ANAM versions of the Go/No-Go task and Running Memory Continuous Performance Task (RMCPT) during baseline (21% O₂) as well as during rest and cycle ergometer workloads that elicited 40 and 60% of adjusted VO₂max in normobaric hypoxia (12.5% O₂). RESULTS: During exercise at 40% and 60% of adjusted VO₂max improved throughput score in RMCPT (p=0.023, p=0.006, respectively) and total mood disturbance (TMD) (p=0.009) compared to rest in hypoxia (p=0.015). In addition there was improved TMD during recovery compare to rest in hypoxia. There is no significant difference in throughput score of RMCPT and TMD between two exercise intensities.
CONCLUSION: The current study demonstrated that at moderate exercise (i.e., 40-60% adjusted VO₂max) attenuated the adverse effects of hypoxia on cognitive performance and mood. This finding may be beneficial for individuals to reduce the risk of impaired cognitive function and mood. Further studies are needed to replicate this current finding, and to clarify the possible mechanisms associated with the potential benefits of exercise on mood state in normobaric hypoxia.
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CHAPTER I
INTRODUCTION

Background

Recreational, occupational, and military activities are often performed in a dynamic and ever changing environment. Individuals often experience multiple environmental stressors at high altitude or hypoxia. At high altitude, a series of physiological adjustments ensue due to a compensatory reduction in oxygen concentration including: changes in ventilation, hemodynamics, hematologic changes, hormone secretions, and metabolism. For instance, at high altitude, individuals who live at sea level are unable to perform physical efforts as much as they can at sea level. In addition to these physiological decrements, exposure to high altitude or hypoxia leads to negative psychological function and mood state. However, the effects of acute exercise on cognitive function in hypoxia are largely unknown.

Above 3,000m of high altitude, there is a substantial reduction of atmospheric pressure associated with hypoxemia (inadequate oxygenation of the blood). Oxygen is the primary element of the human body which is essential for the utilization of energy and to maintain homeostasis. The brain also requires a large amount of oxygen in the blood at all times. The average blood flow of the whole brain needs to be relatively constant at about 50ml/100g/min\(^{-1}\) in man (Lassen, 1974). Also, this average value is unaffected by the normal physiological alternations in brain function related with sleep, intellectual work, muscle movements, or sensory perception (Lassen, 1959) and independent from the changes in cerebral perfusion pressure or arterial blood pressure due
to cerebral auto-regulation. Thus, any compromise may alter cognitive function, mood or homeostasis in general.

Hypoxia is defined as an oxygen deficiency caused by a reduction in the partial pressure of oxygen (PO$_2$) in the ambient air due to ambient barometric pressure (PB) or the oxygen concentration of the inspired air. Cerebral de-oxygenation leads to impaired short-term memory and an increase in reaction time (Du, Li, Zhuang, Wu, & Wang, 1999; Kramer, Coyne, & Strayer, 1993). There are various strategies to reduce the acute mountain sickness (AMS) (e.g. Psychological, operational, and medical strategies), the options for adverse effects are limited in a field operations, and many techniques proposed over the years may not be effective.

Physical exercise such as walking and running may be beneficial for psychological and cognitive function at sea-level. A number of studies have demonstrated that cognitive function improves during a single bout of moderate exercise (J. Brisswalter, Collardeau, & Rene, 2002; T. McMorris, Sproule, Turner, & Hale, 2011). These findings suggest that physiological changes induced by acute exercise have the potential to improve cognitive function. Especially, moderate intensity physical exercise may prevent and/or restore impairment of psychological function. However, the effects of moderate intensity exercise on cognitive function and mood state during hypoxia remain largely unclear.
Purpose of Study

The purpose of the proposed investigation was to examine the following:

1. The effects of hypoxia on metabolic, cerebral blood oxygenation and cognitive function/mood in hypoxia.

2. The effects of moderate intensity exercise on metabolic, cerebral blood oxygenation and cognitive function/mood in hypoxia

Hypothesis

Based on previous studies that it is hypothesized following:

1. Cognitive function and mood state would be impaired while at rest in hypoxia

2. Moderate intensity cycle ergometer exercise would improve and/or restore cognitive function and mood state during exercise in hypoxia
CHAPTER II

REVIEW OF LITERATURE

Physiological Responses to Acute Hypoxia

Hypoxic exposure elicits a number of physiological adjustments to compensate for the reduction in oxygen concentration which may include changes in ventilation, cardiac output, circulation, and blood endocrine levels in an attempt to maintain homeostasis.

The Acute Hypoxic Cardio-respiratory Response

In response to acute hypoxia, respiratory systems are altered immediately and adjust for duration of exposure (Laciga & Koller, 1976). The respiratory system responds to hypoxic exposure with an increase in ventilation initially, followed by a decrease in ventilation. An increase in ventilation can be observed when inspired oxygen pressure ($P_{1O_2}$) decreases below 110 torr or the Partial Pressure of Oxygen ($PaO_2$) is less than 60 torr (Dempsey & Forster, 1982; Laciga & Koller, 1976). The ventilation responses to hypoxia are divided into four ranges of stages. The acute hypoxic ventilatory response (5 to 8 minutes), hypoxic ventilatory depression (about 10 minutes), ventilatory acclimatization (a few hours to days), and hypoxic desensitization (after decades of chronic hypoxic exposure) (Pandolf, Burr, & General, 2002).

The ventilatory responses occur due to a combination of central and peripheral chemoreceptor mechanisms. Change in medullary pH and hydrogen ions ($H^+$) mediate the rate of ventilation. Peripheral chemoreceptor within carotid and aortic bodies promote the
increase ventilation during acute exposure to hypoxia (Dempsey & Forster, 1982). In addition, the hypoxic condition produces lactate in the brain, which could increase H+ concentration near the medullary chemoreceptor (Dempsey & Forster, 1982). During rest at 4,300 meter or 448 torr, partial pressure of alveolar O₂ (PₐO₂) is reduced from 100-104 to 53 torr.

During heavy exercise, arterial oxygen saturation (SpO₂) is slightly reduced from resting values at sea level (Åstrand & Kaare, 1987). Heavy intensity of exercise in hypoxia induces the magnitude of desaturation based on the degree of hypoxia due to an increase in alveolar-arterial PO₂ difference (Fulco, Rock, Trad, Forte, & Cymerman, 1988; Hartley, Vogel, & Landowne, 1973; Sylvester et al., 1981; Wagner et al., 1986). This desaturation can be attributed to either a diffusion limitation (VA/Q relationship) or an increased amount of shunted blood bypassing the oxygenation process (Pandolf, Sawka, & Gonzalez, 1988).

The reduction in maximal oxygen uptake (VO₂max) is observed during acute exposure to altitude above 1,500 meter (720 torr) or breathing with less than 17.5% of oxygen (Grover, Weil, & Reeves, 1986; Squires & Buskirk, 1982; Welch, 1987). There is a minimal decrease in VO₂ max until about 1,500 meter and linear decline of 10% for every additional 1,000 meter of altitude (Buskirk, 1969). Thus, at 4,300 m altitude or breathing a gas mixture about 12.3% oxygen, VO₂max is reduced by an average of 27-28% with a wide range of individual variation (9% to 54%) (Young, Cymerman, & Burse, 1985). Also, there are many factors that influence the reduction in VO₂max such as fitness level, pre-altitude exposure, gender, and altitude duration.
The reduction in VO_{2}\text{max} is related to the amount of oxygen in the arterial blood available to the working muscles because the maximal heart rate, stroke volume, cardiac output and oxygen content of venous blood (CVO_{2}) do not differ from sea level (Fagraeus, Karlsson, Linneranson, & Saltin, 1973; Gleser, 1973; Grover et al., 1986; Hartley, Vogel, & Landowne, 1973; Stenberg, Ekblom, & Messin, 1966). Furthermore, there is a relationship between the degree of reduction in VO_{2}\text{max} and maximal exercise intensity (Fulco, Rock, Trad, Forte, & Cymerman, 1998; Maher, Jones, & Hartley, 1974).

Oxygen uptake or metabolic rate for sub-maximal exercise and rest in acute hypoxia does not differ from sea level (Fulco et al., 1996; Knuttgen & Saltin, 1973; Pandolf et al., 1988). Since VO_{2}\text{max} gradually decreases as altitude increases, it is difficult to perform sub-maximal exercise at the same intensity as altitude than at sea level. Ventilation, heart rate, cardiac output, O_{2}-deficit, O_{2}-debt and lactate accumulation during sub-maximal exercise are higher during hypoxic conditions than normoxic conditions (Åstrand & Kaare, 1987; Fagraeus et al., 1973; Grover et al., 1986; Knuttgen & Saltin, 1973; Stenberg et al., 1966; Welch, 1987).

**Neuroendocrine Response to Acute Hypoxia**

Acute hypoxia alters a number of physiological responses not only respiratory and cardiovascular function but also the endocrine and metabolic function as well. Stimulation of the sympathetic nerve system (SNS) causes sympathetic nerve endings in individual tissues to release epinephrine (EPI) and norepinephrine (NE). During rest in the hypoxic condition, the level of catecholamine is not usually observed until 14-18 hours of exposure.
to 4,300 meter (Fulco, Cymerman, Rock, & Farese, 1985; Maher, Jones, Hartley, Williams, & Rose, 1975). A previous study by Escourrou, Johnson, and Rowell (1984) concluded that 40%, 60% and 75% of VO$_2$max exercise increased in plasma concentration of EPI and NE during the hypoxic condition compared to an ambient air condition. The NE serves as vasoconstrictors and the EPI is vital in carbohydrate (CHO) metabolism in the normoxic condition. The vasoconstrictive properties that NE elicits are largely mediated by the up-regulation via the $\alpha$2c-adrenergic receptors and the depression of the nitric oxide pathway that allows for a dilatory response (Johnson & Kellogg, 2010). But hypoxia may inhibit the local vasoconstriction because of the local vasodilator effect of hypoxemia.

**Regulation of Cerebral Blood flow (CBF)**

The brain needs an adequate amount of oxygen at all times and the average blood flow of the whole brain is relatively constant at approximately 50ml/100g/min-1 in man (Lassen, 1974). Also, this average value is unaffected by the normal physiological alternations in brain function related with sleep, intellectual work, muscle movements, or sensory perception (Lassen, 1959) and independent from the changes in cerebral perfusion pressure or arterial blood pressure due to cerebral auto-regulation (Atkins, Brodie, Rafelt, Panerai, & Robinson, 2010; Iwasaki, Ogawa, Shibata, & Aoki, 2007). Cerebral blood pressure is determined by the balance between the cerebral perfusion and vascular tone (Ogoh & Ainslie, 2009b). However, the mechanism for cerebral blood flow regulation are not fully understood (Secher, Seifert, & Van Lieshout, 2008).
Metabolic Control of CBF

Cerebral blood flow (CBF) increases to deliver an adequate amount of oxygen to keep pace with an increase in cerebral metabolism of the brain during mild to moderate exercise (Secher et al., 2008). The cerebral cortex is activated with dynamic movement, an increase in blood flow to the supplementary motor area and it is termed the primary sensorimotor area of the brain. Researchers have previously reported that cerebral blood flow increased with motor control in an animal model (Gross, Marcus, & Heistad, 1980). In contrast, CBF was reduced with a respiratory stimulant (doxapram), which increased ventilation by stimulation of the peripheral chemoreceptor and exercise although with a similar level of hypocapnia, hypertension, and sympathetic nerve activation was elicited. This study indicated that the vasodilatory effects in brain metabolism override the vasoconstrictor effects of hypocapnia, hypertension, and sympathetic nerves on the cerebral vasculature. Furthermore, Linkis et al. (1995) demonstrated that contraction of right-hand increases middle cerebral artery mean flow velocity (MCA Vmean) in the left MCA (+19%), whereas the increase in MVC Vmean in the right MCA was slight (+4%). However, CBF returns to the baseline level despite additional elevation in cerebral metabolism during heavy exercise (Hellstrom, FischerColbrie, Wahlgren, & Jogestrand, 1996; Moraine et al., 1993). In other words, CBF increases linearly with exercise intensity up to 60% maximal oxygen uptake. Thus, hypocapnia by hyperventilation may be a powerful CBF regulator compared to cerebral metabolism (Ogoh, Dalsgaard, et al., 2005). Higher partial pressures of oxygen improve exercise performance and is associated with increases in cerebral oxygenation rather than muscle oxygenation (Nielsen, Boushel,
Brain O₂ uptake remains unchanged during dynamic exercise at mild to moderate intensities (Ide, Schmalbruch, Quistorff, Horn, & Secher, 2000; Madsen et al., 1993) whereas, brain oxygen consumption increases despite a reduction in CBF at maximal exercise intensities (Ide et al., 2000). Increase in brain O₂ consumption tends to maintain cerebral metabolism by a decrease in CBF by hyperventilation during strenuous exercise. Cerebral metabolic ratio (CMR) is calculated as oxygen uptake / (glucose uptake/lactate uptake/2) and displays change in cerebral metabolism. Secher et al. (2008) demonstrated that CMR decreased as workload increased and is attenuated during and after exercise. This attenuated CMR may reduce exercise performance and induce central fatigue (Dalsgaard et al., 2004; Secher et al., 2008).

Auto-regulation of CBF

Cerebral blood flow is controlled by cerebral auto-regulation (CA). According to Lassen (1959), human CBF is maintained / relatively constant despite mean arterial pressure (MAP) ranging from 60 and 150 mmHg. Ekstromj.B, Nilsson, Linder, and Haggenda.E (1971) reported that auto-regulation has a lower limit and upper limit. The example of lower limit is that CBF decreased during acute hypotension (35 mmHg) in normotensive participants (Finnerty, Witkin, & Fazekas, 1954). But, CBF did not change with mild hypotension (57mmHg) (Mc, 1953). Brys, Brown, Marthol, Franta, and Hilz (2003) examined the effect of dynamic exercise on dynamic CA and demonstrated that exercise does not change CA although exercise modifies the cardiovascular system such as heart rate, arterial blood pressure, and the partial pressure of arterial CO₂ (PaCO₂).
However, diastolic blood pressure and diastolic MCA V were increased from rest to heavy exercise (Ogoh, Fadel, et al., 2005). Also, exhaustive exercise impaired dynamic CA (Ogoh, Dalsgaard, et al., 2005). Therefore, intensive exercise may alter dynamic CA because of the change in cerebral vascular tone.

**Chemical Control of CBF (CO₂ and O₂)**

The partial pressure of carbon dioxide in the blood is an important factor to control CBF and CA (Ide & Secher, 2000). The study by Aaslid, Lindegaard, Sorteberg, and Nornes (1989) demonstrated that hypocapnia induces cerebral vasoconstriction and reduces CBF, whereas hypercapnia increases CBF by cerebral vasodilation, which limits elevations in brain tissue PCO₂. Thus, there is a difference in CBF response between hypo- and hypercapnia. Hypercapnic cerebral CO₂ reactivity overrides hypocapnic CO₂ reactivity. Peebles et al. (2008) reported that there is a large release of nitric oxide (NO) from the brain under hypercapnic condition in humans, whereas this response was absent during hypocapnia. The level of cerebral activation influences the cerebrovascular reactivity to CO₂ because cerebral CO₂ reactivity decreased during sleep (Meadows, Dunroy, Morrell, & Corfield, 2003).

Partial pressure of oxygen (PaO₂) is another important factor to control CBF. Hypoxia and hyperoxia play a role in CBF. At sea level, hyperoxia is associated with a decrease in CBF and decrease in end-tidal PCO₂ (Floyd et al., 2003; Watson, Beards, Altaf, Kassner, & Jackson, 2000). However, hyperventilation decreases PaCO₂ which results in cerebral vasoconstriction and cerebral hypoperfusion (Ainslie et al., 2007). However, the
effect of hyperoxia is not correlated with CBF. The study by Bulte, Chiarelli, Wise, and Jezzard (2007) concluded that regional CBF decreases with a relatively low level of hyperoxia ($F_{O_2} = 0.4$) but, CBF does not gradually decrease with an increase in oxygen concentration ($F_{O_2}=1.0$). Thus, the balance between ventilation and cerebral CO$_2$ reactivity is an important factor for CBF regulation under hypoxic conditions (Ogoh & Ainslie, 2009a).

**Neurogenic Control of CBF**

The control of the cerebral vasculature is different from the peripheral vasculature during rest and exercise. Also, the cerebral vasculature has a small vascular bed and is regulated by CA and PaCO$_2$. In contrast, the peripheral vasculature is modulated by the autonomic nervous system. Sympathetic nerve fibers are mediators and play a small role in the cerebral vasculature (Alm & Bill, 1973; Harper, Deshmukh, Rowan, & Jennett, 1972). However, activation of the sympathetic nervous system leads to cerebral vasoconstriction in hypertensive participants including human and animals (Bill & Linder, 1976; Heistad, Marcus, & Gross, 1978; Patel, Huang, & Sagher, 2003; Rutland, Lee, Nimmon, Granowska, & Britton, 1980). However, stimulation of sympathetic nervous system decreased CBF in severe hypertensive animals even at rest (Heistad et al., 1978). Furthermore, sympathetic nerve activity inhibits vasodilation of the cerebral arterioles (Bill & Linder, 1976; Heistad et al., 1978; Patel et al., 2003; Rutland et al., 1980). Moreover, it is unclear if exercise-induced cerebral vasoconstriction results from elevated sympathetic nerve activity (van Lieshout & Secher, 2008).
Cognitive Performance and Mood State during Hypoxia

The high altitude environment often induces arterial hypoxemia which leads to poor cognitive function and an alteration in mood during hypoxic exposure. Thus hypoxia contributes to dangerous outcomes because affected individuals cannot detect changes by themselves. The degree of hypoxia and arterial hypoxemia is the primary factor for impairment of cognitive function and motor control, personality, and judgment (Crow & Kelman, 1973). When a $P_fO_2$ below 110 torr whereby hemoglobin saturation markedly decreases (Pandolf et al., 1988) physiological homeostasis may change. Several factors are related to performance degradation such as the level of hypoxia, the type of function (motor or sensory), and complexity of task (Crow & Kelman, 1971, 1973; Denison, Ledwith, & Poulton, 1966; Green & Morgan, 1985).

Impairment of psychomotor performance, mental skills, reaction time, vigilance, memory, and logical reasoning have been reported at an altitude of 3,000 meter or above (Bahrke & Shukitthale, 1993). Cudaback (1984) reported that complex cognitive tasks were impaired before simple tasks. Because of these aforementioned studies, we utilized the Automated Neuropsychological Assessment Metrics 4th Edition (ANAM4) in the current experiments. The ANAM4 is a computerized cognitive test battery first developed by the Department of Defense with subtests designed to assess a variety of cognitive domains include mood state.

The subtests will be applied include the Go/No-Go and Running Memory Continuous Performance Task (RMCPT) as well as mood state. GO/No-Go assesses
response inhibition. RMCPT assesses attention, concentration, and working memory. Cognitive function is determined in part by blood flow to the brain. Mood state is designed to assess seven categories of mood; Anger, Anxiety, Depression, Fatigue, Happiness, Restlessness, and Vigor. Near-infrared spectroscopy (NIRS) is a real-time monitor of changes in regional oxygen saturation (rSO\textsubscript{2}) of blood in the brain and is a non-invasive method for the measure of cerebral oxygenation and blood flow (Villringer, Planck, Hock, Schleinkofer, & Dirnagl, 1993).

The sensory functions are affected by altitude before cognitive and psychomotor performance such as vision, hearing, and taste (Banderet, Burse, & Medicine, 1991). Sensory function is impaired at a barometric pressure of 138 torr. Furthermore, a reduction in 10% of central field extent, 30% of central brightness, 34% of dark adaptation and 36% of visual acuity are detected at P\textsubscript{1}O\textsubscript{2} of 86 torr. Impaired vision may be partially responsible for some of cognitive performance (Bullard, Dill, Horvath, & Yousef, 1972). Latency to read (Schlaepfer, Bartsch, & Fisch, 1992) and to detect (Fowler, White, Wright, & Ackles, 1982) visual stimuli increased with hypoxia. Decrease in light sensitivity, visual acuity, and color discrimination can be detected at higher than 3,000 meter (Bullard et al., 1972).

After exposure to high altitude, reduction in ability of speak and comprehension of syntax were observed from five male climbers during the 1993 American Sagarmatha Expedition ascended Mt. Everest (Lieberman, Protopapas, & Kanki, 1995). Exposure to high altitude alters the voice onset time (VOT). The interval between voiced and unvoiced
consonant changed from 24.0 to 5.4 milliseconds (Lieberman et al., 1995) despite normal interval for VOT consonant differ by 20 milliseconds or more. In addition, the longer time was required to understand and speak simple English sentences by 50% at high altitude (Lieberman et al., 1995). They speculated that deficits in speech and motor control and comprehension of syntax are similar to patients with Parkinson's disease due to interruption of sub-cortical pathway in the prefrontal cortex (Lieberman et al., 1995).

Alternations in sensation, symptoms, moods, and physiological functions associated with high altitude have been investigated for many years. Changes in cognitive performance are observed at altitude 3,000 meter or above, whereas changes in sensation, moods, and physiological functions are observed at relatively lower altitudes (McFarland, 1971). At moderate altitude above 4,300 meter, change in the mood state significantly (Shukitt-Hale, Banderet, & Lieberman, 1998) impact cognitive performance (Nebes et al., 2003).

At 4,300 meter, mood state was altered from 2,000 meter after 1 to 4 hours such as friendliness, clear thinking, dizziness, sleepiness and unhappiness and returned to baseline by 2 days. (Shukitt & Banderet, 1988). Furthermore, Shukitt-Hale et al. (1998) evaluated the mood state using the Profile of Mood State and the Clyde Mood Scale during 4.5 hours exposure to 4,200 and 4,700 meter to examine the level and duration of exposure. Seventy-five percent of mood factors (friendliness, sleepiness, dizziness, hostility, depression, anxiety, confusion, fatigue, tension, anger, and vigor) were altered at 4,700 meters but only 25% of mood factors (sleepiness, dizziness, tension, and confusion) were altered at 4,200
meters. The moods were significantly altered only after a few hours of exposure, and the adverse effects increased when exposure was at 4,700 meter compared with 4,200 meter.

**Cerebral Oxygenation and Cognition**

Many physical activities require a high-level of cognitive function during daily life and/or physiological stress. Cerebral de-oxygenation leads to impaired short-term memory and an increase in reaction time (Du et al., 1999; Kramer et al., 1993).

Although Near-infrared spectroscopy (NIRS) appears to underestimate the cerebral oxygenation compared to transcranial Doppler or positron emission tomography (Perrey, 2008), it has become an acceptable, non-invasive method for the measurement of cerebral oxygenation (Villringer et al., 1993). NIRS displays the relative concentration of oxygenated and deoxygenated hemoglobin in red blood cells.

The assessment of cognitive function such as Stroop Color Word Test (SCWT) increases neural activity in various regions of the cerebral cortex as measured by functional magnetic resonance imaging (fMRI). Indeed, dorsolateral prefrontal cortex (DLPFC) (MacDonald, Cohen, Stenger, & Carter, 2000) anterior conglulate cortex (ACC) (Milham, Banich, & Barad, 2003) show increased activity. Endo et al. (2013) found a relationship between the increase in the oxygen-hemoglobin (Oxy-Hb) and the relative percent decrease in total time period for the Stroop test. However, the mechanisms of the relationship have not been determined and are likely not controlled by a single factor (i.e., prefrontal Oxy-Hb) post-exercise.
Exercise, Mood states, and Cognitive function

Over the past several years, the relationship between exercise and brain cortical activity (Crabbe & Dishman, 2004), mood state (Schneider, Askew, et al., 2009; Schneider, Brummer, Abel, Askew, & Struder, 2009) and cognition (Hillman et al., 2009) have been studied using different exercise intensities (Hall, Ekkekakis, & Petruzzello, 2010), duration (Woo, Kim, Kim, Petruzzello, & Hatfield, 2009), and exercise modes (Schneider, Askew, et al., 2009). The effects of exercise on cognitive function may depend on intensity and duration of the exercise. Exercise at 40% of VO$_2$ max for 15min using a cycle ergometer significantly improved Stroop test scores (Endo et al., 2013). Dynamic exercise at 60% of VO$_2$ max for 3.5 min also improved the reaction time of the Erikson flanker task (Ando, Kokubu, Yamada, & Kimura, 2011). However, 5 min of exercise duration did not improve the Stroop time score with the same intensity of exercise (40% of VO$_2$ max) and longer than 1 hour of exercise induces thermogenesis and elicits central fatigue which thereby impairs cognitive function (Blomstrand, Hassmen, Ekblom, & Newsholme, 1991; Hancock, 1986). Furthermore, the time point between the end of exercise and beginning of the Stroop test is critical to evaluate because 5 min following exercise this time period did not demonstrate cognitive improvements (Endo et al., 2013). However, exercise activates the central nervous system (CNS) and psychomotor performance improves with activation of the CNS. The choice reaction time decreases until exercise intensity about 75% VO$_2$max and dramatically increases exceeding the anaerobic threshold (Chmura, Nazar, & Kaciuba-Uscilko, 1994). A moderate intensity exercise below lactate threshold may improve cognitive function whereas high intensity exercise may lead to an impaired cognitive function.
function (J. Brisswalter et al., 2002). Thus, intensity of exercise is highly related with the alternation of the central nervous system.
CHAPTER III

METHODOLOGY

Participants

The Institutional Review Board at Kent State University approved this study and all subjects signed a consent form prior to participation. Nineteen young healthy men volunteered for the current investigation. Participants were screened for eligibility by using a medical history questionnaire and written informed consent was obtained prior to participation. All participants were free of pulmonary disease, cardiovascular disease, postural orthostatic tachycardia syndrome, skeletal muscle injury in their lower limbs and were not exposed to normobaric hypoxia or an altitude above 2500m within two months prior to the study.

Experimental Design

Figure 1 provides an overview of the experimental protocol. All subjects participated in two experimental trials. Subject underwent a pre-experimental testing session and a hypoxia experimental session on separate day.

Pre-Experimental Testing (Session 1)

Prior to participation, participants were introduced to the hypoxic chamber and familiarized with the protocol and instrumentation. During this time the participants were made fully aware of the risks and commitments required by the investigation.
Participants were then asked to complete a consent form and medical history questionnaire.

After completion of documentation, anthropometric measurements (height, weight, and body fat content), resting blood pressure and heart rate were assessed. Participants then performed 2 cycling protocols during which the participants breathed through a mouth-piece attached to the metabolic cart. The first protocol involved 3 four minutes stages at sub-maximal intensities of 50, 100 and 150 watts. The second protocol was a VO₂ max test which required them to pedal on the cycle ergometer through increasing stages of intensity until volitional fatigue to estimate ventilatory threshold (VT) and maximal oxygen consumption (VO₂ max). This test started off at 20 watts and increased by 25 watts every minute (Amann, Subudhi, & Foster, 2004). VO₂ max and peak HR were recorded. The combination of these two protocols allowed the determination of VO₂ max and the determination of cycling power required to elicit 40% and 60% VO₂ max during the subsequent visit.

VO₂ max test was conducted on a magnetic braked cycle ergometer (Lode Excalibur, Groningen, Netherlands). The expired air was analyzed for oxygen and carbon dioxide concentration using an automated open circuit system (Parvo Metabolic Cart, Sandy, Utah) to determine VO₂ max and VT (Yoon, Kravitz, & Robergs, 2007). VT was determined by VE/VO₂ increase to detect anaerobic threshold (Caiozzo et al., 1982).
A VO₂max decreases by approximately 27% from sea-level value at 4,300 meter (Fulco et al., 1998; Young et al., 1985). Exercise intensity was 40% and 60% of adjusted VO₂ max which is a 27% reduction of VO₂max from sea-level.

**Experimental Procedure**

**Baseline testing.** Participants reported to the Exercise Physiology Lab at Kent State with at least a 3 hour fasted status. The participant sat on a chair for 30 minute at which time they were equipped with a heart rate monitor, Near-Infrared Spectroscopy (NIRS) sensors and pulse-oximeter, followed by determination of resting metabolic rate. Expired air samples (VO₂ and VCO₂) and heart rate (HR) were obtained by an indirect open circuit spirometry system (Parvo, Metabolic Cart, Sandy, Utah) and a Polar heart rate monitor (Polar RS800 CX, Polar Electro Oy, Kempele, Finland). Frontal lobe cerebral oxygenation was monitored via Near Infrared Spectroscopy (NIRS) (Somanetics, Troy, MI). Systolic, diastolic, and mean arterial pressure (MAP) were obtained by an auscultatory method (sphygmomanometer and stethoscope) with the participant’s left arm at heart level.

Furthermore, Cognitive function and mood state were measured at predetermined time points via a computerized test battery. The cognitive function and mood state measured using Automated Neuropsychological Assessment Metrics- 4th Edition (ANAM4). The ANAM 4 is a computerized cognitive function test battery with subtests designed to assess a variety of cognitive domains. Specific subtests utilized include the Mood state, Running Memory continuous performance Task (RMCPT), and Go/No-Go.
The mood state provides seven categories including anger, anxiety, depression, fatigue, happiness, restlessness, and vigor with range from 0 "not at all" to 6 “very much”.

RMCPT measured sustained attention, concentration and working memory. Go/No-Go assesses response inhibition. Following a baseline phase, Participants entered into an environmental chamber, within which the partial pressure of inspired oxygen (PaO₂) was 159 torr (760 mmHg pressure * 20.95% oxygen) or partial pressure of inspired oxygen (PaO₂) was 98.8 torr (760 mmHg pressure * 12% oxygen). The 12.5 % of oxygen was equivalent to the oxygen level of altitude of 4300 meters (14,110 feet). They then sat on the nylon-mesh chair for 60 minutes. All hypoxia testing occurred in a hypoxia chamber (Colorado Altitude Training, CO). Several physiological and psychological measurements were obtained including VO₂, HR, MAP, rSO₂, SpO₂, Go/No-Go, RMCPT, mood state, and RPE.

During resting period, VO₂, BP, HR, SpO₂, rSO₂, RPE, Go/No-Go, RMCPT, mood state and RPE were obtained from minute 26-33 and 57-63.

After the resting period, the individuals were instructed to sit on the cycle ergometer (Ergomedic 828E, Mornak, Swenden). Then the participants performed two 15 minute bouts of cycle ergometry at 40% and 60% of VO₂max with a 15 minute recovery period following each bout. Exercise intensity was counterbalanced. Again, all of the aforementioned measurements were performed during the final 7 minutes of each exercise and recovery stage.
After the trial, participants exited the hypoxic chamber and rested on a chair until their arterial oxygen saturation returned to baseline levels.

**Statistical Analysis**

SPSS version 17.0 was utilized to conduct the statistical analysis. First, one-way repeated measures ANOVA was utilized for the mean reaction time and correct response of Go/No-Go task and mean reaction time, correct response and throughput score of Running Memory Continuous Performance Task, VO$_2$, BP, HR, SpO$_2$, and rSO$_2$ across condition (Baseline, Rest, 40% and 60%). When the ANOVA indicated a significant main effect, paired sample t-tests were utilized to determine where those differences existed. Second, a two group (40%, 60%) by four time point (Baseline, Rest, Exercise, Recovery) repeated measures ANOVA was conducted for total mood disturbance, anger, anxiety, depression, fatigue, happiness, restlessness, vigor, SpO$_2$ and RPE. If a significant interaction was found, post-hoc paired-sample and independent sample t-test was used. In addition, paired sample t-test and independent sample t-test were conducted separately when a main effect was found. For TMD, happiness, vigor, cerebral oxygenation and SpO$_2$, paired sample t-test was used to determine the main effect for time. Independent sample t-test was used for RPE. For fatigue, independent sample t-test and paired sample t-test were used to determine the main effect for group and time. Data are presented as mean ± SD and the level of significance was set a priori at $p \leq 0.05$. 
CHAPTER IV

THE INFLUENCE OF EXERCISE ON COGNITIVE PERFORMANCE IN NORMOBARIC HYPOXIA

Abstract

Although previous reports indicate that exercise improves cognitive function in normoxia, the influence of exercise on cognitive function in hypoxia is unknown. The purpose of this study was to determine if the impaired cognitive function in hypoxia can be restored by low to moderate intensity exercise.

Sixteen young healthy men completed the ANAM versions of the Go/No-Go task (GNT) and Running Memory Continuous Performance Task (RMCPT) in normoxia to serve as baseline (B-Norm) (21% O₂). Following 60 minutes of exposure to normobaric hypoxia (B-Hypo) (12.5% O₂), these tests were repeated at rest and during cycling exercise at 40% and 60% of adjusted VO₂max.

At B-Hypo, the % correct (p≤0.001) and throughput score (p≤0.001) in RMCPT were significantly impaired compared to B-Norm. During exercise at 40% (p=0.023) and 60% (p=0.006) of adjusted VO₂max, the throughput score in RMCPT improved compared to B-Hypo, and there was no significant difference in throughput score between the two exercise intensities. Mean reaction time also improved at both exercise intensities compared to B-Hypo (p≤0.028). Both peripheral oxygen saturation (SpO₂) and regional cerebral oxygen saturation (rSO₂) significantly decreased during B-Hypo (p≤0.001) and
further decreased at 40% (p≤0.05) and 60% (p≤0.039) exercise. There was no significant difference in SpO$_2$ or rSO$_2$ between two exercise intensities.

These data indicate that low to moderate exercise (i.e., 40-60% adjusted VO$_2$max) may attenuate the risk of impaired cognitive function that occurs in hypoxic conditions.
Introduction

Cognitive function while at altitude plays an important role in optimizing performance and safety during work and recreational activities. Due to the reduced partial pressure of oxygen, high altitude environments often induce arterial hypoxemia (Auerbach & Geehr, 1989) which leads to poor cognitive function (Crow & Kelman, 1973). Specifically, impairment of psychomotor performance, mental skills, reaction time, vigilance, memory, and logical reasoning has been reported at altitudes of 3,000 meters and above (Bahrke & Shukitt-Hale, 1993; Crow & Kelman, 1971; Denison et al., 1966). Cudaback (1984) reported a reduced ability to perform complex cognitive tasks in hypoxia before a compromised ability to perform simple tasks. This cognitive dysfunction can easily lead to dangerous outcomes especially considering individuals may be unaware of their compromised cognitive state. Therefore, developing a countermeasure to restore and/or improve cognitive function at altitude would likely reduce an individual’s vulnerability to accidents.

Interestingly, previous studies have indicated that cognitive function is mediated by brain cortical activity (Crabbe & Dishman, 2004) which can be positively influenced by exercise. The improvements in cognitive function depend on the intensity (Hall et al., 2010) and mode (Schneider, Askew, et al., 2009) of exercise. For example, the choice reaction time, a test used to assess psychomotor speed (Overton et al., 2011), decreases as exercise intensity increases up to 75% VO$_2$max, with further increases in exercise intensity resulting in an increased reaction time (Chmura et al., 1994). These results are further supported by J. Brisswalter, Arcelin, Audiffren, and Delignieres (1997) who reported that
moderate intensity exercise below lactate threshold can improve choice reaction time whereas high intensity exercise leads to impaired cognitive function (J. Brisswalter et al., 2002). Chmura, Krysztofiak, Ziemba, Nazar, and Kaciuba-Uscilko (1998) also reported that during a sub-lactate threshold exercise protocol, choice reaction time decreased through the first 40 min of exercise after which choice reaction time remained constant for the remainder of the 60 minute exercise protocol. Thus, it is possible that exercise, at low to moderate intensities, can also improve cognitive function in hypoxic conditions.

A better understanding of the interaction between cognitive performance and exercise in a hypoxic condition could prove beneficial to promote the health and performance of those who work and play in such conditions. To our knowledge, improvements of cognitive performance have been observed during sub-maximal exercise (low to moderate intensities) by several investigations in normoxia. However, few studies investigated the effect of acute exercise on cognitive function in hypoxia. As such, the purpose of this investigation is to focus solely on hypoxic condition to determine if the impaired cognitive function in hypoxia can be restored by low to moderate intensity exercise by comparing physiological responses and indices of cognitive function during rest, and at 40% and 60% adjusted VO$_2$max in hypoxic conditions. Based on aforementioned previous literature, it was hypothesized that cognitive function in hypoxic conditions would decrease during rest in hypoxia, however exercise at both 40% and 60% VO$_2$max would improve and/or restore cognitive function.
Methods

The Institutional Review Board at Kent State University approved this study and all subjects signed a consent form prior to participation. Sixteen young healthy men (24±4 years of age; height=176.5±6.5cm and weight=78.3± 9.4kg) volunteered for the current investigation. All participants were free of pulmonary disease, cardiovascular disease, postural orthostatic tachycardia syndrome, skeletal muscle injury in the lower limbs and were not exposed to normobaric hypoxia or an altitude above 2500m within two months prior to participation in the study.

Experimental Procedures

Each participant reported to the laboratory on two separate occasions (familiarization trial and experimental trial). During the familiarization trial, participants underwent pre-screening and were introduced to the simulated altitude chamber. Subjects were also familiarized with the protocol and instrumentation including performing the cognitive function tests a minimum of three times. Participants then performed 2 exercise protocols on a cycle ergometer (Lode Excalibur Sport, Lode, Groningen, Netherlands) to determine the sub-maximal exercise intensities that would be used during the subsequent experimental trial. The first protocol required them to pedal through 3-four min stages at 50, 100, and 150 watts to develop their VO₂-workrate relationship. Upon completion of the first protocol, participants rested for at least 20 minutes. The second protocol was a VO₂max test which required participants to pedal on the cycle ergometer through increasing stages of intensity, starting at 20 watts and increasing by 25 watts every minute (Amann et al., 2004) until volitional fatigue. During both protocols VO₂ and HR were
measured with a metabolic cart (Parvo, Sandy, Utah) and a Polar heart rate monitor (Polar RS800 CX, Polar Electro Oy, Kempele, Finland), respectively. The combination of these two protocols allowed for the determination of VO\textsubscript{2}max as well as the power output required to elicit 40% and 60% VO\textsubscript{2}max, which was ultimately reduced by 27% for the experimental trial to adjust for the VO\textsubscript{2}max decrements with altitude (Fulco et al., 1998; Young et al., 1985). The adjusted 40% and 60% exercise intensities were selected as they span the range of exercise intensities previously reported to improve cognitive function at sea level (Arcelin, Delignieres, & Brisswalter, 1998b; Reilly & Smith, 1986; Tomporowski, 2003).

On the day of the experimental trial (Figure 2), participants reported to the Exercise Physiology Laboratory at Kent State University following a 3 hours fast. Participants were initially equipped with a HR monitor, mouthpiece for the metabolic cart, Near-Infrared Spectroscopy (NIRS) sensors over the frontal lobe (Somanetics, Troy, MI) for regional cerebral oxygen saturation (rSO\textsubscript{2}) monitoring and digit pulse-oximeter (Oxi-Go, Roslyn, NY) for peripheral oxygen saturation (SpO\textsubscript{2}) measurement. Subjects sat on a chair quietly during 5 minute baseline recordings of resting metabolic rate, blood pressure, heart rate, SpO\textsubscript{2}, and rSO\textsubscript{2}. GNT and RMCPT were conducted via a computerized test battery.

Following baseline measurements (B-Norm) participants entered the hypoxic chamber (Colorado Altitude Training, Louisville, CO) where the oxygen concentration was reduced to 12.5% with similar increases in %N\textsubscript{2} but no changes in %CO\textsubscript{2}. The 12.5%O\textsubscript{2} is equivalent to the oxygen level present at an altitude of 4300 meters (14,110
feet). The room temperature and relative humidity in the hypoxic chamber were consistently 22-24°C and 30-40% throughout testing. After resting on a chair for 60 min in the hypoxic chamber cerebral oxygenation, VO₂, HR, SpO₂, were recorded and GNT and RMCPT were administered to obtain hypoxic baseline measurements (B-Hypo).

**Sub-maximal Bouts of Exercise**

Following the completion of hypoxic baseline measurements, the participants performed two 15 min bouts of cycle ergometry at 40% and 60% of adjusted VO₂max with 15 min recovery period between bouts. The pedaling rate (revolution per min) was freely chosen but workload was maintained automatically and exercise intensities were counterbalanced. All aforementioned measurements were performed during the final 5 min of each exercise stage (min 11-15). The 15 min recovery period was chosen based on previous studies indicating the effects of exercise on cognitive function dissipates within a few minutes following cessation of exercise (Audiffren, Tomporowski, & Zagrodnik, 2008, 2009; Labelle, Bosquet, Mekary, & Bherer, 2013). Upon completion of the hypoxia trial, participants stepped out of the hypoxic chamber and rested until their SpO₂ returned to baseline levels.

**Cognitive Task Measurement**

Cognitive function was assessed through administration of specific subsets of the Automated Neuropsychological Assessment Metrics-4th Edition (ANAM4), a computerized cognitive performance test battery consisting of variety of cognitive domains. The ANAM4 has been administered to military and sports-related concussion, exposure to
radiation, high altitude, undersea, and toxic conditions (Bleiberg et al., 2004; Eonta et al., 2011). The specific subtests utilized in this study include the GNT and RMCPT. The GNT was designed to assess response inhibition where participants were instructed to click the left mouse button as quickly as possible in response to an “X” stimulus on the monitor that was presented at random intervals. If the monitor displayed “O” stimulus, they were instructed not to click the mouse button. The RMCPT performance measured short-term memory whereby participants were instructed to discriminate between two response alternatives (left or right button) if the displayed number matched or did not match the preceding number, respectively. The % correct and throughput scores were recorded. The throughput score was calculated as: Throughput score = accuracy / response time.

**Data Analysis**

Using SPSS 17.0, one-way repeated measures ANOVA was utilized for mean reaction time and correct response of GNT and mean reaction time, correct response and throughput score of RMCPT, VO2, BP, HR, SpO2, and rSO2 across conditions (baseline, resting, 40% and 60%). When the ANOVA indicated a significant main effect, post hoc comparisons were utilized to determine where those differences existed. The level of statistical significance was set at alpha ≤ 0.05 and all data are presented as mean ± SD.

**Results**

The average VO2max was 46.9±7.7 and adjusted VO2max was 34.3±5.6 ml/kg/min. The corresponding workload of 40% and 60% was 52±16 and 101±23 Watts, respectively.

**Cognitive Measurements**
**Go/No-Go Task.** The reaction time and % correct in GNT demonstrated no significant main effect for condition ($F= 1.8, p=0.168$), ($F=2.2, p=0.098$), respectively (Fig. 3A and 3B).

**Running Memory Continuous Performance Task.** The reaction time in RMCPT demonstrated a significant main effect for condition [$F= 3.4, p=0.025$]. The reaction time in RMCPT was not impaired at B-Hypo compared to B-Norm ($p=0.180$). However, during 40% and 60% of exercise, reaction time significantly improved compared to B-Hypo ($p=0.028$ and $p=0.009$, respectively). Also, during 40% and 60% of exercise, reaction time did not differ compared to B-Norm ($p=0.256$ and 0.08, respectively) (Fig. 4A).

The % correct in RMCPT demonstrated a significant main effect for condition ($F=7.6, p≤0.001$). An impairment of % correct in RMCPT was observed at B-Hypo compared to B-Norm ($p≤0.001$). % correct in RMCPT during 40% and 60% of adjusted exercise intensity was also significantly different from B-Norm ($p=0.001$, $p=0.001$, respectively). Furthermore, % correct in RMCPT was not different between any of the hypoxic conditions (B-Hypo, 40% and 60% exercise) ($p>0.262$) (Fig. 4B).

Throughput score (Accuracy/Response time) in RMCPT demonstrated a main effect for condition ($F= 5.0, p=0.005$). Throughput score in RMCPT was significantly lower at B-Hypo compared to B-Norm ($p≤0.001$). Following B-Hypo, 40% and 60% of exercise intensity improved performance ($p=0.023$ and 0.006, respectively) and were not significantly different compared to B-Norm ($p=0.676$ and 0.522, respectively). There was
no significant difference in throughput score between exercise intensities (p=0.329) (Fig. 4C).

**Physiological Measurements**

The dependent variables MAP, HR, and VO₂ showed main effects for condition (F= 16.2, p≤0.001), (F= 185.8, p≤0.001), and (F= 206.1, p≤0.001), respectively (Fig 5A-C). As expected, significantly higher MAP, HR, and VO₂ were observed during both 40% and 60% of exercise compared to B-Norm (p<0.05) and B-Hypo (p<0.05). Furthermore, all cardio-respiratory parameters were significantly different between 40% and 60% bouts of exercise (p<0.05).

Regional cerebral oxygen saturation demonstrated a main effect for condition (F = 196.9, p≤0.001). Average of both left and right rSO₂ was significantly reduced at B-Hypo compared to B-Norm (p≤0.001). After 60 min resting in hypoxia, 40% and 60% of adjusted exercise further decreased cerebral oxygenation compared to B-Hypo (p=0.05 and 0.04, respectively). There was no effect of exercise intensity in cerebral oxygenation (p=0.752) (Fig. 6A).

SpO₂ revealed a main effect for condition (F= 225.2, p≤0.001). SpO₂ decreased during the B-Hypo condition (p≤0.001) compared to B-Norm. Following B-Hypo, SpO₂ was further reduced significantly during 40% and 60% of exercise (p≤0.001, for each comparison) compared to B-Hypo. Similarly, SpO₂ was not different between the two exercise intensities (p=0.824) (Fig. 6B).

**Discussion**
We hypothesized that cognitive performance (i.e., GNT and RMCPT) would be impaired after 60 min of resting in hypoxia, but exercise at 40% and 60% of adjusted VO$_2$max would restore and/or improve the performance to near normoxic values. The findings of this study were: (1) 60 min of hypoxia exposure in a resting condition resulted in partially impaired cognitive function; (2) low and moderate exercise performed in hypoxia partially restored and/or improved cognition; and (3) there was no significant difference between the two exercise conditions on improving cognition. These data indicate that low to moderate exercise (i.e., 40-60% adjusted VO$_2$max) likely attenuates the risk of impaired cognitive function that ensues in hypoxic conditions.

**Cognitive and Physiological Measurements at Rest in Hypoxia**

Previous investigators have reported that cognitive function was impaired after 60 min of hypoxia exposure and complex cognitive tasks were impaired before simple tasks (Adam, Fulco, & Muza, 2008; Cudaback, 1984; Hewett, Curry, Rath, & Collins, 2009; Kryskow, Beidleman, Fulco, & Muza, 2013). The data supports these previous investigations in that partial impairments of cognitive performance were observed during at the B-Hypo time point compared to B-Norm. Specifically, we did not observe a significantly impaired mean reaction time and % correct in GNT which is a relatively simple task based primarily on motor reaction time. However the % correct and throughput score of RMCPT are more complex tasks as it is influenced by reaction time as well as attention, concentration, and working memory. Our data indicate a significantly impaired % correct and throughput score of RMCPT at the B-Hypo compared to B-Norm. It appears a speed-accuracy trade off, with fewer correct responses and unchanged or slightly
increased mean reaction time during both GNT and RMCPT. The results from both GNT and RMCPT are in agreement previous studies, indicating that participants made more errors and increased mean reaction time in hypoxic conditions (Van Diest, Stegen, Van de Woestijne, Schippers, & Van den Bergh, 2000). Another previous study supports these findings in that reaction time and correct responses were decreased on the Word-Color Stroop task (Asmaro, Mayall, & Ferguson, 2013).

As expected, SpO$_2$ and rSO$_2$ were decreased significantly at B-Hypo compared to B-Norm. Kryskow et al. (2013) observed that after 8 and 30 hours of altitude exposure, SpO$_2$ decreased compared normoxic conditions (78±8 and 79±6, respectively). Furthermore, Gomes, Matsuura, and Bhambhani (2013) reported that after 5-10 min of hypoxia exposure (12-15% Fraction of inspired O$_2$) SpO$_2$ was reduced at rest in healthy subjects. In this investigation, other physiological measurements (HR, MAP, and VO$_2$) were not significantly different compared to baseline.

**Cognitive and Physiological Measurements during Exercise in Hypoxia**

The mean reaction time and % correct of GNT were not improved during either 40% or 60% exercise intensities compared to B-Hypo. However, the mean reaction time and throughput score of RMCPT during the two exercise conditions were significantly improved compared to B-Hypo. Furthermore, there was no significant difference in cognitive function between the two exercise intensities. The results from the RMCPT are in agreement with previous studies, indicating that dynamic exercise at low to moderate intensities of short duration improve cognitive function in normoxia (Ando et al., 2013; Arcelin, Delignieres, & Brisswalter, 1998a; J. Brisswalter et al., 1997; J Brisswalter,
Durand, Delignieres, & Legros, 1995; Quelhas Martins, Kavussanu, Willoughby, & Ring, 2013). The present study observed exercise intensities of 40% and 60% of VO$_2$max, thus these intensities are suitable for eliciting improvements in cognitive function in hypoxic environments as well.

All physiological measurements were statistically different between two exercise intensities including HR, VO$_2$, and MAP with the highest values being obtained during the 60% condition. These results are to be expected during the higher exercise intensity as a greater metabolic demand, induces a greater physiological response. Interestingly, during both 40% and 60% VO$_2$max exercise, both cerebral oxygenation and SpO$_2$ were reduced compared to the B-Hypo (Figure 5). This decrease in cerebral oxygenation and peripheral oxygen saturation with exercise and partial improvement, or at least maintenance of cognitive performance indicates that oxygen saturation and cognitive function becomes dissociated under hypoxic conditions. There are several possible explanations for the improvement in cognitive function despite a reduction in rSO$_2$ and SpO$_2$. First, exercises stimulate the central nervous system (CNS) which ultimately improves psychomotor performance (Chmura et al., 1994). Several investigations suggested that improvements of cognitive performance result from adjustment of brain neurotransmitter such as dopamine, noradrenaline, serotonin, and adrenocorticotropic (ACTH) with onset of exercise (Davranche & Audiffren, 2004; Terry McMorris, 2009; Tomporowski, 2003). Another possible explanation is that exercise induces arousal which improves cognitive function (Lambourne & Tomporowski, 2010). The exercises also increase in production of cortisol which inhibits the synthesis of corticotrophin and ACTH. As exercise intensity and
duration increase, arousal levels also increase until cognitive performance is limited by strenuous exercise (Lambourne & Tomporowski, 2010). More research is needed to elucidate which mechanisms may be offsetting the decrease in cerebral oxygenation.

The current study is limited by a few factors. First, this study recruited only young Caucasian men. Hence, a more diverse range (e.g., gender, age, and ethnicity) need to be evaluated to generalize the results. Second, it might be beneficial to assess unaltered VO$_{2}$max values or absolute power values and exercise intensity in the hypoxic condition. Lastly, additional measurement of physiological parameters (e.g., middle cerebral artery, sympathetic nerve activity) and pharmacological/nutritional strategies could be used for future experiments to assess the cause-and-effect mechanism and determine if cognitive performance correlated to physiological parameters.

**Conclusion**

The present study is the first to reveal that impaired cognitive function resulting from hypoxic environments can be partially restored by acute exercise. Impairments of cognitive performance resulting from the hypoxic environment may be important for individuals who participate in sports events and work at altitude. Although modern equipment and medications are well designed and useful to protect one from hypoxia, exercise performance and cognitive function cannot be sustained with these ergogenic aids. The present findings, therefore, suggest that low to moderate intensity exercise (40% - 60%) does not further reduce cognitive function and likely may be benefit individuals
performing intellectual tasks in the hypoxic condition and may reduce the risk associated with any potential impairment in cognitive function.
CHAPTER V

DOES EXERCISE IMPROVE MOOD STATE IN NORMOBARIC HYPOXIA?

Abstract

Exposure to high altitude or hypoxia produces negative mood states in many individuals. This may place the individuals at undue risk, as negative mood state is related to decrease military performance and decrements in mental abilities. Exercise at 40% and 60% VO\textsubscript{2}max has previously been shown to improve psychological and mood state at normoxia but little is known about its effect in hypoxia. The purpose of this study was to quantify the effects of two exercise intensities on mood state in normobaric hypoxia. 19 young, healthy men completed ANAM versions of the mood state test before hypoxia exposure, after 60 minutes of hypoxia exposure (12.5% O\textsubscript{2}), and during and after two intensities of cycling (40% and 60% VO\textsubscript{2}max) under the same hypoxic conditions. Peripheral oxygen saturation (SpO\textsubscript{2}) and regional cerebral oxygen saturation (rSO\textsubscript{2}) were continuously monitored. At rest in hypoxia, Total Mood Disturbance (TMD) was significantly increased compared to baseline in both Low and Moderate groups (p=0.002). TMD was significantly decreased during exercise compared to rest in hypoxia (p=0.009). TMD was also significantly decreased during recovery compared to rest in hypoxia (p=0.015). Peripheral oxygen saturation significantly decreased at 60 min rest in hypoxia, during exercise, and recovery compared to baseline (p≤0.001 for all comparisons). Regional cerebral oxygen saturation was also reduced at 60 min rest in hypoxia, during exercise, and recovery compared to baseline (p≤0.001 for all comparisons). The current study demonstrated that exercise at 40% and 60% of adjusted
VO_{2}\text{max} attenuated the adverse effects of hypoxia on mood. This finding may have significant applied value, as negative mood states are known to impair performance in hypoxic condition. Further studies are needed to replicate the current finding, and to clarify the possible mechanisms associated with the potential benefits of exercise on mood state in normobaric hypoxia.
Introduction

Monitoring mood state is important for everyday activities and sports performance, as well as occupational activities. Transient mood state is related to many cognitive functions and mental process such as planning, attention, decision making, working memory, problem-solving and behavior control (Aoki et al., 2011; Lane, Terry, Stevens, Barney, & Dinsdale, 2004; Mitchell & Phillips, 2007; Terry, 1995). At high altitudes, especially above 4,300m there is a marked reduction in positive mood state and concurrent increases in negative mood state (Shukitt-Hale et al., 1998). Specifically, vigor decreases with an increase in fatigue and seven physical symptoms (i.e., cerebral acute mountain sickness (AMS), respiratory AMS, cold, distress, exertion, muscular discomfort and fatigue) (Shukitt-Hale et al., 1998). This agrees with previous study by de Aquino Lemos et al. (2012) who reported that levels of depression, anger, and fatigue to be significantly higher and vigor significantly lower at altitude (de Aquino Lemos et al., 2012).

There have been numerous studies that have observed the beneficial effects of acute bouts of exercise performed in normoxic conditions on mood state (Bartholomew, Morrison, & Ciccolo, 2005; Ekkekakis, Hall, VanLanduyt, & Petruzzello, 2000; Andrew Steptoe & Bolton, 1988; A. Steptoe & Cox, 1988). An acute bout of exercise performed at 60% VO\textsubscript{2}max for 10 min promoted vigor, decreased fatigue and negative mood state. In addition Hansen, Stevens, and Coast (2001) reported that confusion was attenuated during 20 min of exercise. A review paper by Yeung (1996) reported that moderate intensity (50-70% VO\textsubscript{2}max) exercise improved mood state such as anxiety, vigor, and
exhilaration. Also, Ekkekakis et al. (2000) reported that exercise duration in excess of 10-15 min may have a positive impact on mood state. However, very little is known about the mechanisms in which exercise enhances mood state and if they can counteract or abolish the mood depressing effects observed in a hypoxic environment. As such, the purpose of this study was to quantify the effects of exercise on mood state at rest, during exercise and recovery in hypoxic conditions. It is hypothesized that mood state in hypoxia would be impaired following 60 min of exposure at rest, but would be improved during two cycle ergometer exercise intensities (40% and 60% VO$_{2\text{max}}$) and recovery.
Methods

Participants

Nineteen young healthy Caucasian men volunteered for the current investigation and reported to the laboratory on two separate occasions (familiarization and hypoxia trial) separated by at least three days. Through completion of a medical history screening, participants with a history of medical, neurological, developmental, or psychiatric disorders were excluded. The participants were assigned as either Low (40% VO₂max) or Moderate (60% VO₂max) exercise intensities. The separation of two groups was selected to minimize exposure to hypoxia, boredom and possible learning effects. The study protocol was approved by the Institutional Review Board at Kent State University. All participants were given written informed consent form before participating. The physical characteristics of the participants are displayed in Table 1.

Experimental Procedures

Each group of participants underwent a pre-screening followed by an experimental session in a thermoneutral environment (22-24°C). On the first day, participants were introduced to the simulated altitude chamber and familiarized with the protocol and instrumentation including performing the mood state tests a minimum of three times. Participants also conducted 2 cycling protocols on a Lode Excalibur 1300W ergometer (Lode Excalibur Sport, Lode, Groningen, Netherlands) to determine the sub-maximal exercise intensities that would be used during the subsequent experimental trial. The first protocol required participants to pedal through 3-four min stages at 50, 100, and
150 watts to determine their VO2-workrate relationship. Upon completion of the first protocol, participants rested for at least 20 min or until their HR returned to baseline. The second protocol was a VO2max test which required participants to pedal on the cycle ergometer through increasing stages of intensity until volitional fatigue to estimate ventilatory threshold (VT) and maximal oxygen consumption (VO2max). The max test began at 20 watts and increased by 25 watts every min until volitional fatigue of the participant (Amann et al., 2004). During both protocols VO2 and HR were measured with indirect open circuit spirometry (Parvo, Metabolic Cart, Sandy, Utah) and a Polar heart rate monitor (Polar RS800 CX, Polar Electro Oy, Kempele, Finland). The combination of these two protocols allowed the determination of the power output required to elicit 40% and 60% of an altitude specific adjusted VO2 (Fulco et al., 1998; Young et al., 1985) during the subsequent visit.

On the day of the hypoxia trial, participants reported to the Exercise Physiology Laboratory at Kent State University following a 3 hour fast. Participants were initially equipped with Near-Infrared Spectroscopy (NIRS) sensors over the frontal lobe (Somanetics, Troy, MI) and digit pulse-oximeter (Oxi-Go, Roslyn, NY). Subjects sat on a chair quietly during the 5 min baseline measurement of Mood State (MS), Peripheral oxygen saturation (SpO2), regional cerebral oxygen saturation (rSO2) and rating of perceived exertion (RPE).

Following baseline measurements, participants entered the hypoxia chamber where the oxygen concentration was “set” at 12.5% and had resulting similar increases in %N2 but no changes in the %CO2. The 12.5%O2 is equivalent to the oxygen level
present at an altitude of 4300 meters (14,110 feet). Participants rested on a chair for 60 min. Mood state, SpO$_2$, rSO$_2$ and RPE were administered from min 57-60. Upon completion, the individuals were instructed to sit on the cycle ergometer.

**Sub-maximal Exercise Bout**

As depicted in Fig 7. The participants performed 15 min bouts of exercise on the cycle ergometer at either 40% or 60% of adjusted VO$_2$max followed by a 15 min recovery period. Each group was assigned in a counterbalanced fashion. Mood state, SpO$_2$, rSO$_2$ and RPE were again measured during the final 7 min of exercise and following the recovery period. Upon completion of the measurements, participants were removed from the hypoxia chamber.

**Mood State Measurements**

Mood state (MS) were assessed with Automated Neuropsychological Assessment Metrics-4th Edition (ANAM4). The ANAM4 mood state is designed to assess seven categories of mood; anger, anxiety, depression, fatigue, happiness, restlessness, and vigor. Specifically, through the use of a tablet, 42 words expressing various emotions were presented to the subject and they were instructed to choose a number between 0 and 6 with 0 being “Not at all” and 6 being “Very Much” for each emotion presented. These emotions are associated with the seven categories of mood state.

**Data Analysis**

Using SPSS 17.0, a two group (40%, 60%) by four times point (Baseline, Rest, Exercise, Recovery) repeated measures ANOVA was conducted for total mood
disturbance as well as the seven categories of mood state: anger, anxiety, depression, fatigue, happiness, restlessness, vigor, SpO2 and RPE. If a significant interaction was found, post-hoc paired-sample and independent sample t-test was used. In addition, paired sample t-test and independent sample t-test were conducted separately when a main effect was found. For TMD, happiness, vigor, cerebral oxygenation and SpO2, paired sample t-test was used to determine the main effect for time. Independent sample t-test was used for RPE. For fatigue, independent sample t-test and paired sample t-test were used to determine the main effect for group and time. Data are presented as mean ± SD and the level of significance was set a priori at p ≤ 0.05.

Results

Total Mood Disturbance

Total Mood Disturbance (TMD) was calculated as negative mood (anger, anxiety, depression, fatigue and restless) subtracted by positive mood (happiness, vigor). TMD demonstrated a main effect for time (p≤0.002), but no main effect for group (p=0.240) and no main effect for time by group interaction (p=0.103). Therefore, for all subsequent analysis the 40% and 60% groups were combined into one group. Baseline TMD values were similar between groups (Low: -73.8±71.1 vs. Moderate: -52.9±33.1, p=0.432). TMD increased at 60 min rest in hypoxia compared to baseline (p=0.002) and decreased during exercise compared to 60 min rest in hypoxia (p=0.009). Further, TMD was significantly decreased during recovery compared to 60 min rest in hypoxia (p=0.015) (Fig 8).
Individual Mood State

Individual two-way repeated measures ANOVA indicated that anger, anxiety, depression and restless did not show a main effect for group, time, and group by time interaction (P≥0.05). However, fatigue demonstrated a main effect for time (p=0.001) and group by time interaction (p=0.025) but no main effect for group (p=0.592). Independent sample t-test revealed that fatigue was significantly higher in the Moderate group during exercise compared to Low group (Low: 7.6±9.5 vs. Moderate: 17.4±8.6, p=0.031). Within the low group, fatigue was significantly increased at 60 min rest in hypoxia compared to baseline (p=0.05). Fatigue subsequently decreased during exercise (p=0.019) and recovery (p=0.029) compared to 60 min rest in hypoxia. Fatigue within the Moderate group did not differ across time points (p>0.05). Both Happiness and Vigor demonstrated a main effect for time (P≤0.032) but no main effect for group (p≤0.321), and no main effect for group by time interaction (p≤0.397). Thus for these two categories of mood state, the 40% and 60% groups were combined into one group for all subsequent analysis. Happiness decreased at 60 min rest in hypoxia compared to baseline (P=0.006) but happiness did not significantly improve during exercise compared to 60 min rest in hypoxia (p=0.602). Vigor decreased at 60 min rest in hypoxia compared to baseline (p=0.002) and vigor significantly increased during exercise and recovery compared to 60 min rest in hypoxia (p≤0.001 and p=0.006, respectively) (Table 2).

Arterial oxygen saturation and Cerebral oxygenation

Peripheral oxygen saturation and regional cerebral oxygen saturation demonstrated a main effect for time (p≤0.001), but no main effect for group (p=0.969), and no main
effect for group by time interaction (p=0.534). Again, for all subsequent analysis the 40% and 60% groups were pooled into one group. SpO$_2$ significantly decreased at 60 min, exercise, and recovery in hypoxia compared to baseline (p≤0.001 for all comparison). During exercise SpO$_2$ further decreased compared to 60 min rest (p≤0.001). After cessation of exercise, SpO$_2$ was significantly increased compared to exercise (p≤0.001) (Fig 9). Regional cerebral oxygen saturation significantly decreased at 60 min, exercise, and recovery compared to baseline (p≤0.001 for all comparison). During exercise, cerebral oxygenation decreased compared to 60 min rest (p≤0.001). During recovery, cerebral oxygenation significantly increased compared to exercise (p≤0.001) (Fig 10).

RPE was significantly higher during exercise in the Moderate group compared to the Low group (p=0.05). RPE was significantly increased during exercise in both Low and Moderate group (p≤0.001 and p=0.009, respectively) compared to 60 min rest in hypoxia. Several physiological parameters may have caused impairment and improvement in mood state at rest, exercise, and recovery. Exploratory correlation did not significantly relate cerebral oxygenation and TMD across time points. SpO$_2$ and TMD also did not show a significant correlations (p>0.05).

Discussion

The purpose of this study was to quantify change in mood state during rest, exercise and recovery in hypoxia. We hypothesized that mood state would be negatively impacted during the resting in hypoxia and exercise at 40% and 60% of VO$_2$ max and would improve overall mood state. The data from this investigation support our
hypothesis in that TMD increased in hypoxia at rest, but was reversed both during exercise and recovery from exercise. Cerebral oxygenation, however cannot explain the changes in total mood state as cerebral oxygenation decreased with hypoxia and further decreased during exercise.

Along with TMD, the individual categories of mood were also compared across conditions. Across the 4 conditions, we observed no change in anger, anxiety, depression, and restlessness. However, we observed an increase in fatigue and decrease in happiness and vigor at 60 min of rest in hypoxia. This is in agreement with a previous study in which impaired fatigue and vigor was experienced during acute exposure to hypoxia (Shukitt-Hale et al., 1998). Furthermore, Shukitt and Banderet (1988) reported that friendliness, clear thinking, dizziness, sleepiness and unhappiness were affected at 1 and 4 h after ascent to 4300m. A study by Li et al. (2000) suggested that negative mood (tension, fatigue, and confusion) increased and the positive mood (vigor) decreased during the hypoxia exposure for 1 h. Those results slightly conflict ours in that, depression and anger did not increase with exposure to hypoxia.

Exercise in hypoxia significantly improved vigor and fatigue compared to the resting condition. Fatigue was significantly higher in the Moderate (intensity) group compared to Low (intensity) group during exercise. Furthermore, RPE was higher in the Moderate group during exercise compared to the Low group. This result is to be expected during the higher exercise intensity, as a greater stress, induces more perceptional/perceptual responses (Scherr, Wolfarth, Pressler, Wagenpfeil, & Halle, 2011).
Average of both left and right cerebral oxygenation as well as SpO₂ were significantly decreased at 60 min of rest in hypoxia and further decreased during exercise. This is in agreement with previous studies that cerebral oxygenation decreased during low-intensity exercise in hypoxia (Imray et al., 2005; Subudhi, Dimmen, & Roach, 2007). This decrease in cerebral oxygenation and SpO₂ with exercise and improved TMD indicates that although these two variables may be related in resting conditions across various levels of hypoxia, exercise dissociates these two variables. There are likely some other stimulating factors involved with exercise that offset the decrease in cerebral oxygenation. Subsequent research in this area may consider, additional physiological measurements (i.e., cerebrovascular function, sympathetic nerve activity), to better predict mood state for future experiments.

**Conclusion**

Caution should be taken when one attempts to predict health related symptoms and physical or psychological performance during hypoxia. The monitoring of mood state is important in optimizing performance and safety during work and recreational activities during normobaric hypoxia. Based on the data presented from the present investigation, single bouts of exercise between 40-60% VO₂max appears to be beneficial to partially improve impaired mood state (vigor and fatigue) in hypoxia. Further research is needed in this area to elucidate the mechanism underlying the improvement in mood state.
To our knowledge, few studies have investigated the effect of acute exercise on cognitive function and mood state in hypoxia. The purpose of the present study was to determine if the impaired cognitive function and mood state in hypoxia can be restored by moderate intensity exercise during exercise and recovery.

The impairments of cognitive performance resulting from the hypoxic environment were seen at 60 min rest in hypoxia. However, impaired cognitive performances were partially improved with moderate intensity exercise (40% - 60%). It is important to note that moderate intensity exercise would be beneficial for individuals who must perform intellectual processes in a hypoxic condition and would most likely reduce the risk associated with any potential impairment in cognitive function.

Similarly, mood state was negatively impacted during rest in hypoxia. During exercise in hypoxia between 40-60% of VO2max mood state (vigor and fatigue) was partially enhanced. It is important to note that the monitoring of mood state is crucial in optimizing performance and safety during work and recreational activities during normobaric hypoxia.

Cognitive function and mood state improved with moderate intensity exercise despite the reduced cerebral oxygenation were decreased. Thus, future research is necessary to determine if perceptual parameters would correlate to impairments or improvement of cognitive and mood state to establish a prediction model. Moreover,
additional measurements of physiological parameters and pharmacological/nutritional strategies could be used for future experiments to assess the cause-and-effect mechanism and to determine if cognitive performance correlated to selected physiological parameters.
Figure 1 Experimental design and timeline of study.

Pre-experimental testing and experimental testing. Participants will perform two 15 minute bouts of cycle ergometry at 40% and 60% of VO\textsubscript{2max} with a 15 minute recovery period following each bout. Exercise intensity will be counterbalanced. All measurements will be performed during the final 8 minutes of each exercise and recovery stage.
Figure 2 Experimental Design and procedure.

Pre-experimental session (upper) and experimental session (lower), Shaded grey area occurred in hypoxic condition
Figure 3 Mean reaction time (A) and % correct in Go/No-Go (B) at baseline, following 60 minutes of rest in hypoxia and during exercise at 40% and 60% VO$_2$max in hypoxia. Everything to the right of the vertical dashed line occurred in hypoxic conditions. There were no statistical differences across the 4 conditions.
Figure 4 Mean reaction time (A), % correct (B) and throughput score (C) in running memory continuous performance task at baseline, following 60 minutes of rest in hypoxia and during exercise at 40% and 60% VO$_2$max in hypoxia.

Everything to the right of the vertical dashed line occurred in hypoxic conditions.*Means with the same letters are significantly different from each other.
Figure 5 Mean arterial pressure (A), heart rate (B) and oxygen consumption (C) at baseline in normoxia, following 60 minutes of rest in hypoxia and during exercise at 40% and 60% VO$_2$max in hypoxia.

Everything to the right of the vertical dashed line occurred in hypoxic conditions. *Means with the same letters are significantly different from each other.
Figure 6 Averaged of regional cerebral oxygen saturation (A) and peripheral oxygen saturation (B) at baseline in normoxia, following 60 minutes of rest in hypoxia and at 40% and 60% VO₂max in hypoxia. 

Everything to the right of the vertical dashed line occurred in hypoxic conditions. *Means with the same letters are significantly different from each other.
Figure 7 Experimental design and procedure. Shaded grey area occurred in hypoxic conditions.
Table 1 Physical characteristic between groups

<table>
<thead>
<tr>
<th></th>
<th>Low (n=10)</th>
<th>Moderate (n=9)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO(_2)max (ml/kg/min)</td>
<td>48.3±8.6</td>
<td>45.2±6.6</td>
<td>0.441</td>
</tr>
<tr>
<td>AdjVO(_2)max (ml/kg/min)</td>
<td>35.3±6.3</td>
<td>33.0±4.8</td>
<td>0.443</td>
</tr>
<tr>
<td>HRmax (beats/min)</td>
<td>183±13</td>
<td>185±13</td>
<td>0.781</td>
</tr>
<tr>
<td>40%Watts</td>
<td>58±16</td>
<td>43±13</td>
<td>0.234</td>
</tr>
<tr>
<td>60%Watts</td>
<td>107±23</td>
<td>93±22</td>
<td>0.064</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24±3</td>
<td>25±4</td>
<td>0.905</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177±4.8</td>
<td>175.6±8.6</td>
<td>0.634</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.4±11.4</td>
<td>78.1±6.9</td>
<td>0.949</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.
Table 2 Mood State of participants at baseline, 60 minutes of rest, exercise and after exercise in hypoxia

<table>
<thead>
<tr>
<th>Sub-scale</th>
<th>Baseline</th>
<th>60 min</th>
<th>Exercise</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Mood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger</td>
<td>2.1±5.0</td>
<td>3.7±6.3</td>
<td>3.0±4.8</td>
<td>3.7±6.1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4.3±6.8</td>
<td>6.3±8.1</td>
<td>3.5±4.6</td>
<td>4.6±5.6</td>
</tr>
<tr>
<td>Depression</td>
<td>2.6±5.6</td>
<td>4.3±7</td>
<td>3.1±5</td>
<td>2.9±4.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16±14.3</td>
<td>25.3±23.3*</td>
<td>12.3±10.2##</td>
<td>11.6±13.5#</td>
</tr>
<tr>
<td>Restless</td>
<td>6.4±7.9</td>
<td>8.8±10.8</td>
<td>6.7±8.2</td>
<td>7.4±9.5</td>
</tr>
<tr>
<td>Positive Mood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Happiness</td>
<td>60.4±23.5</td>
<td>51.1±21.1*</td>
<td>52.8±19.6</td>
<td>56.3±22.1</td>
</tr>
<tr>
<td>Vigor</td>
<td>43.4±22.9</td>
<td>31.5±18.3*</td>
<td>48.3±20.7##</td>
<td>47.6±23.3#</td>
</tr>
</tbody>
</table>

Participants responded to the question at each time point, “How much do the following words describe how you feel right now? Data are presented as mean ± SD.

*p<0.05 versus at baseline, #p<0.05 versus at 60 min rest in hypoxia
Figure 8 Change in Total Mood Disturbance, Negative Mood, and Positive Mood at baseline, 60 min rest, exercise and recovery in hypoxia.

Shaded grey area occurred in hypoxic conditions. *Means with the same letter are significantly different at all variables.
Figure 9 Change in peripheral oxygen saturation at baseline, 60min, exercise and recovery in hypoxia.

Shaded grey area occurred in hypoxic conditions. *Means with the same letter are significantly different.
Figure 10 Change in regional cerebral oxygen saturation at baseline, 60min, exercise and recovery in hypoxia.

Shaded grey area occurred in hypoxic conditions. *Means with the same letter are significantly different.
APPENDIX A

LETTER OF CONSENT
Informed Consent to Participate in a Research Study

Study Title: *The effects of acute exercise on cognitive performance in hypoxic condition*

Principal Investigator: *Ellen Glickman, Ph.D.*

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**
Cognition impairments have been reported during exposure to hypoxia (low oxygen) in humans. However, moderate intensity exercise at sea level has been shown to increase cognition. Therefore, the purpose of the current investigation is to determine exercise at moderate intensity can offset the reduction in cognition that occurs in hypoxia.

**Procedures**
Prior to participation, participants will be screened for eligibility using health and medical history questionnaire. Inclusion/exclusion criteria for the volunteers include the following: 1) participants must be 18-30 years old and 2) must not have pulmonary disease, cardiovascular disease, postural orthostatic tachycardia syndrome, skeletal muscle injury in lower limb or must not be pregnant. To ensure your concerns/questions are addressed appropriately the primary investigator and at least one other co-investigator will be present during the consent process and study protocols.

This investigation will require you to visit the exercise physiology laboratory on two separate occasions. The first is to become familiar with the study procedures and partake in some baseline measurements. Visit 2 will require you to perform some exercise in a
hypoxic (low oxygen environment). The hypoxic condition is set to resemble what you would experience at 14,000 feet or at Pike’s Peak Colorado. The specific visits are described below.

**Visit 1:** On the initial visit you will be required to read and sign the consent from if you are willing to participate in the study. At that point you will be asked to complete a health history questionnaire and we will take a series of measurements including your height, weight and skin folds measurements to determine your % body fat. You then be asked to perform 2 cycling protocols. The first will require you to pedal the ergometer through 3 four minute stages. Although the intensity increases with each stage, all three stages are submaximal. The next cycling protocol is VO₂max tests which will require to you pedal the bike for roughly 8-12 minutes. The intensity will start off very easy and progressively get harder and you will be encouraged to continue until you can no longer pedal the bike. You are encouraged to continue cycling until you reach volitional fatigue or until you can no longer maintain a cycling cadence of 60 rpm. During both test you will be breathing into a tube so the metabolic cart can measure the amount of oxygen you consume. Following a recovery period you will be familiarized with several of the tests you will perform on visit 2. These tests will not be scored on the first visit, rather they are presented so you become familiar with them.

**Visit 2:** The figure above illustrates the protocol for visit 2. For this visit you must report to the laboratory after a 3 hour fasting period (you can drink water during this time).

Initially you will be equipped with several sets of electrodes. Near-Infrared spectroscopy (NIRS) electrodes will be attached on your forehead to monitor brain tissue oxygenation. Pulse-Oximeter will be used to measure oxygen saturation (SpO₂) in the arterial blood using a clip on your index finger. A heart rate monitor will be placed around your chest to monitor heart rate. These variables will be continuously monitored. The trial will last for 2 hours. This will include 1 hours of resting in a chair, two-15 minutes bouts of cycling exercise on a stationary bike followed by 15 minute recovery periods sitting in a chair. The intensity of the exercise will be 40% and 60% of VO₂ max which was
determined on the initial visit. At multiple time points throughout this protocol we will ask you to breathe through a mask so we can measure your metabolic rate. At these times we will also ask you to perform a series of cognitive function tests on a computer, each test taking approximately 3 minutes. The time points in which we will be collecting this data are marked by the bold arrows in the figure above. When the protocol is complete, you will be able to leave the chamber, however you cannot leave the exercise physiology lab until your SpO₂ returns to baseline levels. This usually takes no more a minute.

Once these protocols start, exiting the chamber will result in termination of the test. You may or may not wish to reschedule. Thus, prior to starting these protocols we will encourage you to use the restroom.

**Benefits**
The potential benefits of participating in this study may include ability to have data on your aerobic fitness and we will be able to categorized your fitness level based on national standard and prescribe exercise training if they score indicate poor cardiovascular fitness. In addition, some individual are sensitive to hypoxia (i.e. headache and dizziness). Exposure to the short term hypoxia will provide some evidence with regard to how well you can tolerate this environment. This may impact travel or vacation plan (i.e. going to mountain of Colorado to ski).

**Risks and Discomforts**
This study involves one bout of maximal exercise and several bouts of submaximal exercise. As with all physical activity, you may become fatigued, lightheaded, short of breath during the exercise and muscular soreness post exercise. There is also the risk of cardiovascular event, however these risks are minimal as you must be a young healthy, physically active young individual to partake in this investigation. While in the hypoxic environment, you will likely have increased ventilation rate, heart rate and become lightheaded which may be slightly uncomorting. Although acute mountain sickness usually peaks after 18 hours of exposure to hypoxia, there is a possibility that you may also develop a headache. If this becomes too uncomfortable or intolerable, please let us know and we will stop the test and you can leave the chamber. These symptoms will reside shortly after you leave the chamber.

To minimize risks associated with the hypoxic condition, we will follow the standard operation procedure (SOP) for hypoxic chamber and will record your SpO₂ level before, during and after hypoxic exposure on log book and if SpO₂ falls below 72% the test will be terminated and we will remove you from the chamber.
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**
No compensation will be given for the completion of the aerobic fitness test (visit 1). A $25 gift card will be provided to you for participating in visit 2. This gift card will be provided to you regardless of whether you are able to complete the entire protocol during visit 2.

**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. Furthermore, participation in this investigation will have no influence on your academic success. To minimize the risk for coercion, you cannot be recruited or consented by one of the investigators if they are also one of your class instructions.

**Contact Information**
If you have any questions or concerns about this research, you may contact Ellen Glickman at (330-672-2930) or (Yongsuk Seo at 330-805-1342). 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 FORM
Appendix B

Health History Form

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 BY THE INVESTIGATORS AND RESEARCH PERSONNEL

Name__________________________________________  Date____/____/____

Date of Birth____/____/____  Present Age____ yrs

Ethnic Group:  ____White

____ African American
____ Hispanic
____ Asian
____ Pacific Islands
____ American Indian
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.

<table>
<thead>
<tr>
<th>YEAR</th>
<th>OPERATIONS OR ILLNESS</th>
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<table>
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<th>YEAR</th>
<th>OPERATIONS OR ILLNESS</th>
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<th>YEAR</th>
<th>OPERATIONS OR ILLNESS</th>
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</table>

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

____ Other __________
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 (phlebitis)
[ ] 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)
<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
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</thead>
<tbody>
<tr>
<td>Have you ever passed out during or after exertion?</td>
<td></td>
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<tr>
<td>Do you have a family history of coronary artery disease</td>
<td></td>
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</tr>
<tr>
<td>If yes, Who? (Grandparents, parents, siblings, uncles, and aunts)</td>
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<tr>
<td>Are there any other reasons not mentioned above that you feel you should not participate in this research study?</td>
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<tr>
<td>Do you currently smoke cigarettes?</td>
<td></td>
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<tr>
<td>Do you currently use any smokeless tobacco products?</td>
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Appendix C

Data Sheet

Anthropometric characteristics

# Subject: ___________ Date: ___________
Age: _______ (years) Gender: _____ (M/F)
Height: ___________ (ft/in or cm) Weight: _________ (lbs/kg) BMI: ______
RHR: ___________ Max HR: ___________ Blood pressure: ___________
MAP: ___________ mmHg (=1/3 *(SBP-DBP) + DBP)

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<thead>
<tr>
<th>Skin fold (mm)</th>
<th>Average</th>
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<tr>
<td>Subscapular</td>
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<tr>
<td>Chest</td>
<td></td>
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<tr>
<td>Side</td>
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<tr>
<td>Suprailium</td>
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<td>Abdomen</td>
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<td>Thigh</td>
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%BF = ___________

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<td>Calf</td>
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<td>Waist</td>
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<td>Hip or buttock</td>
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Sum = ___________
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<th>60min Rest</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Exercise</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Recovery</th>
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10.1152/japplphysiol.00606.2002


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