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Hypoxic Stress in Athletes With Sickle Cell Trait

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HYPOXIC STRESS IN ATHLETES WITH SICKLE CELL TRAIT

By

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Bachelor of Science in Athletic Training
West Virginia University
2014

A Thesis submitted in partial fulfillment of the requirements for the

Master of Science – Kinesiology

Department of Kinesiology and Nutrition Sciences
School of Allied Health Sciences
Division of Health Sciences
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Thesis Approval

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Hypoxic Stress in Athletes with Sick Cell Trait

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ABSTRACT

HYPOXIC STRESS IN ATHLETES WITH SICKLE CELL TRAIT

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The purpose of this study was to examine various changes of blood measures in select athletes with sickle cell trait due (SCT) to exercise at different simulated altitudes (n=2). Previous studies have determined that athletes with sickle cell trait have complications in diminished oxygen environments, along with the potential for a lower oxygen carrying capacity with exertion. The study used a Hypoxico Altitude Training System in order to alter the oxygenated environment, and the subjects were evaluated at 2,470, 5,000 and 8,370 feet elevations. Arterial oxygen saturations were measured with pulse oximetry. The study demonstrated that these athletes with sickle cell trait had arterial oxygen saturation percentages consistent with those of a hypoxic nature throughout an exercise bout.

ACKNOWLEDGEMENTS

I would like to thank my parents for their unending support and express how much I appreciate their kind words throughout this process.

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CHAPTER 1

INTRODUCTION

Sickle cell trait (SCT) has received an overwhelming amount of attention in the last 10 years, and it has become a factor to consider in conditioning practices for individuals that can possibly suffer from sickling crises.¹ Even though the muscles look and feel like normal, the adverse sensation of a sickling crisis will come in the form of a severe, ischemic type of muscle pain, stemming from the muscles lacking adequate blood supply.² Athletes that deal with SCT, an abnormal hemoglobin gene, can experience adverse effects such as muscle cramping and inability to sustain endurance activities every time they are at a high level of exertion regardless of altitude, but the likelihood of presentation of symptoms become more severe with the addition of exertion at altitude.

Since the first football death attributed to SCT in 1974,^{1,3} this condition has been widely recognized as a serious risk for sickling crises precipitated by high intensity endurance activity. The rate of sickling varies, not only with the amount of abnormal sickled hemoglobin (HbS) in red blood cells, but also with sport participation, climate, and each individual's fitness and conditioning level.⁴ Individuals with sickle cell trait are not excluded from sports participation, as this condition is separate from and cannot develop into the more severe sickle cell disease. However, the National Collegiate Athletic Association (NCAA) made it mandatory for all Division 1 athletes to be screened for this condition prior to participation.⁵ This mandate was made following a wrongful death suit filed by the parents of Dale Lloyd, a Rice University football player who collapsed and later died due to complications from an unknown sickle cell trait gene.⁵

A sickling crisis can cause grave consequences for athletes suffering from them. These crises are characterized by an increased ratio of hemoglobin S, a specific type of hemoglobin that is more sensitive to the effects of unloading oxygen. When the oxygen is unloaded, hypoxia ensues to allow these cells to distort their shape, which causes them to abnormally clot the vessels, leading to vascular emergencies.⁶ In particular, competition at altitude presents a serious challenge to the athlete with SCT because of the added strain on the cardiovascular system from hypoxia.⁷ However, there is little evidence on the response of athletes with SCT in this environment. Therefore, the purpose of this study is to evaluate the sensitivity of athletes with a diagnosed SCT condition at various altitudes.

Aim

1. To examine various changes of blood measures in select athletes with sickle cell trait (SCT) due to exercise at simulated altitudes.

Significance of Study

Physiologically, athletes competing at altitude struggle with the atmospheric changes, mainly due to their increased Hemoglobin S being more sensitive to the unloading of oxygen. This increased sensitivity paired with a lack of initial oxygen carrying capacity can precipitate a sickling crisis.³ There is currently a lack of knowledge concerning the interaction of different altitudes and exercise on athletes with sickle cell trait.

Limitations

A key limitation in this study was the limited sample size. Unfortunately, within the university population utilized, there are typically a limited number of athletes that are affected by this gene, so participants were scarce. Another limitation was that all participants were female limiting the results to only half of the affected population. Also, several uncontrollable factors also came into play, such as athlete's hydration that affected the blood drawing process.

CHAPTER 2

REVIEW OF RELATED LITERATURE

A normal red blood cell (RBC) is disc shaped, and has the oxygen carrying protein, hemoglobin (Hg). RBCs lifespan is about 120 days in the blood stream. The spongy bone marrow's function is to make new red blood cells to replace old and dysfunctional cells.^{8,9}

Each hemoglobin molecule is made up of four sub-units that have a heme group and a globin molecule. Two alpha subunits are bound to two y-subunits in the fetus' hemoglobin, and the y-subunits turn into beta subunits in an adult hemoglobin molecule. The alpha globin chain is found on Chromosome 16 and the beta globin is part of Chromosome 11. The sickled hemoglobin, HbS, is formed when there is a point mutation in the 6th position of the amino acid codon where valine is substituted for glutamic acid in the beta chain.¹⁰ Red blood cells that contain mostly HbS have a tendency to become stiff, distorted in shape, and as a result, can have great difficulty passing through small blood vessels.⁶ This abnormal chromosome causes a 40% presence of sickled hemoglobin in the blood of SCT individuals.⁴ SCT causes red blood cells to have a significantly shorter life span of 10-20 days, as opposed to the 120 days of normal red blood cells.⁸ SCT is characterized by anemia and recurrent episodes of painful small blood vessel obstruction by rigid, sickle-shaped red blood cells accompanied by inflammation and vascular adhesive processes.¹¹

There is a SCT prevalence of about 8% among African Americans, and is much less common in Caucasian individuals, between 1 in 2,000 and 1 in 10,000 individuals.⁴ The populations aside from the African American population affected by SCT, accounting for only 4% of carriers, will most likely be of Mediterranean, Middle Eastern, Indian, South American, or Central American descent.⁴

In order to understand the pathophysiology of sickling, Eichner³ states that a “sickling foursome” has been used in an attempt to explain what is happening at the cellular level. The metabolic acidosis and hyperthermia in the cells cause a right shift of the oxygen dissociation curve. When the red blood cells become dehydrated, there is an increase in hemoglobin S, sickled hemoglobin. There is also an effect of severe hypoxemia because of the sudden maximal uptake of oxygen by the muscles. The presence of hypoxia and falling pH of the blood causes HbS to polymerize, which distorts the red blood cell shape.³

When a shift occurs in the oxygen dissociation curve, it is termed the Bohr effect, and it assists the unloading of oxygen from the hemoglobin in the blood molecules that are passing through active muscles.⁹ Red blood cells are composed of glycolytic enzymes, and also contain the enzyme diphosphoglycerate mutase (2,3-DPG). During exercise, these specific enzymes are inflated, particularly during exertion at high altitude. When 2,3-DPG binds to hemoglobin, it causes a rightward shift of the oxygen dissociation curve, decreasing hemoglobin affinity for oxygen.⁹

According to Katch, McArdle and Katch,¹² hemoglobin is very sensitive to temperature and acidity, which are two of the factors of the sickling foursome. The binding of oxygen to hemoglobin is affected when either of these two conditions is modified. Both oxygen and carbon dioxide are able to bind to hemoglobin, and these molecules compete for the heme binding sites, with the one of highest concentration usually winning out. In situations where there is an increase of carbon dioxide, the blood becomes more acidic. When arterial blood is delivered to working muscle, carbon dioxide produced by muscle alters the affinity of hemoglobin for oxygen and oxygen is released to the muscle. Changes in temperature in muscle produce a similar result. The working muscles will produce heat when producing ATP. This increase in temperature

causes a right shift in the hemoglobin-oxygen dissociation curve, causing the binding of oxygen to decrease. This increase in temperature and decrease in pH is known as the Bohr effect, which states that as temperature and acidity increase, hemoglobin's ability to bind decreases.¹²

Sickled red blood cells (RBCs) exhibit a potassium leak to shear stress, which is further increased at lower pH levels. Deformation of RBCs during the adhesion of sickled hemoglobin can induce this potassium leak, and make the polymerization of HbS worse. Hypoxia, decrease in pH and deformation of RBCs in muscles can increase this efflux of potassium. With the continuum of the sickling and efflux of potassium, severe hyperkalemia can ensue, putting the individual in grave danger of sudden death.⁶

Vascular function in SCT athletes is also impaired, although still raises some questions on its specific physiology. Nitric oxide (NO) is one of the most potent, naturally occurring vasodilators in the body, and a decrease in its availability causes endothelial dysfunction.¹³ Minimal research has been conducted to examine plasma NO levels between SCT athletes and healthy individuals, and have found only small reductions in NO concentration in SCT individuals.¹³ The small amount of data available does not offer a clear answer of the vascular mechanisms, other than overall endothelial dysfunction due to distorted cells.¹³

Other occurrences for the vaso-occlusive crises are increased RBC aggregation, increased strength of RBC aggregates, increased blood viscosity and increased plasma level in vascular cell adhesion molecules (VCAM-1).¹³ When the muscles are being robbed of their needed oxygen, ischemia occurs. This ischemia typically appears as pain, and is most common in high vascular areas, such as long bones (due to bone marrow), spine, chest, and abdominal region.¹⁴

Cleary¹⁵ describes how sickle cell trait increases an affected athlete's chance for sudden death during exertion. In terms of collapse for SCT athletes, there are several factors that are

common in many sickling episodes. Athletes will typically collapse while running, sometimes at altitude, sometimes for very short (300-800m) distances lasting less than three minutes, and almost always occurring at an athlete's maximal intensity.¹⁵ Between 1977 and 1981, the rate of sudden unexplained death in black military recruits with SCT was 28 times higher than black recruits without SCT.¹⁵

A sickling crisis comes with some unique signs and symptoms, as compared to other conditions such as muscle cramping. Eichner³ describes several notable differences between these two conditions. First, with heat cramping, there are often preceding events leading up to an episode. Minutes to hours before a cramping episode, the athlete may see or feel their muscles start to twitch. With a sickling crisis, there are no preceding symptoms. The pain felt between a cramping athlete and sickling athlete will also be different. A cramping pain is normally an excruciating type of pain, as compared to a milder pain felt in a sickling athlete. The sickling athlete will complain of feeling weak, and no longer be able to hold themselves up. The cramping athlete will no longer be able to move due to full contraction of the muscles. On physical observation, sickling and cramping will also vary. In heat cramps, the muscles will be in full contraction, and cause extreme pain. A sickling athlete typically lays still and complains mostly of their legs both in pain and being weak, but their muscles will look and feel like normal. Finally, the response to treatment will be different. The athlete who is sickling will be able to return to a pre-crisis state after about 10-15 minutes in a cold tub, replacing fluids and receiving supplemental oxygen if necessary. It will only take this long for the sickling athlete due to the red blood cells returning to their previous oxygenated state. With a heat cramping athlete, this can last up to an hour, even with the athlete resting, replacing fluids, and stretching.³

There are several complications associated with SCT. Connes et al¹⁶ reported impaired autonomic nervous system activity in carriers, implicating that carriers could be predisposed to cardiovascular problems. Exercise at high altitude can increase the athlete's risk for a splenic infarction due to the large amounts of sickled cells into this organ.¹¹ SCT may increase the risk for renal medullary carcinoma, hematuria, and exercise related sudden death. SCT is found predominantly in individuals with ancestry in sub-Saharan Africa where malaria is prevalent. The genetic adaptation for SCT provides protection against malaria.¹⁷ It has also been found that there is an increased risk for venous thromboembolism in females that use hormonal contraceptives and have SCT.¹⁷ Several sources state a trend of SCT and exertional rhabdomyolysis being linked.^{15,18} Rhabdomyolysis is defined as a muscle breakdown and consequential release of muscle toxins into the circulation.¹⁵ The aftermath of a sickling crisis can cause conditions such as metabolic acidosis, myoglobinuria, hyperkalemia, elevated plasma enzymes, renal failure, and "sudden death" within 48 hours.¹⁵ The possible sequelae of myoglobinuria is a sign that rhabdomyolysis was very likely linked to the sickling crisis. There have been several studies on SCD patients, and the muscle biopsies done in order to determine the extent of damage at the cellular level. Several muscle biopsy results showed necrosis of myocytes and occlusion of blood vessels¹⁶ as well as several inflammatory cells present, which is very similar to autopsies done on SCT athletes that died following strenuous exercise. This also shows a connection between a sudden sickling death and the leakage of toxic myoglobin into the blood, in this case affecting the myocytes.

In order for an athlete to become accustomed to the altitude, they must become acclimatized, which typically takes about 10-20 days. The proper production of erythropoietin can make this acclimatization time more beneficial. Erythropoietin, or EPO, is a hormone that

acts on the bone marrow in order to produce new red blood cells. With the increased number of red blood cells comes an increase in oxygen carrying capacity in the blood. Athletes performing at altitudes of 12,000 feet or higher must be acclimatized. However, those participating in short duration, explosive activities have no immediate need for this acclimatization period.¹⁹

As an individual ascends to higher altitudes, the atmospheric (barometric) pressure starts to decrease which results in less oxygen per volume of air.⁹ According to the Institute for Altitude Medicine,¹⁹ high altitude starts at around 5,000 feet. At this altitude, the body starts to sense a climate and oxygen change and increases the individual's breathing rate accordingly. As an individual begins to ascend, the atmospheric pressure starts to decrease. The percentage of oxygen in the air remains a consistent 21%, however, that 21% value is taken from a smaller value since there is less oxygen per volume.²⁰ Due to this decrease in the partial pressure of oxygen, performance is decreased at higher altitudes.¹⁹ When athletes ascend to higher altitudes, the partial pressure of oxygen decreases, which corresponds to a decrease in the arterial pressure of oxygen, leading to tissue hypoxia.²¹ As altitude increases, there is also a reduction in alveolar oxygen pressure and arterial oxygen saturation resulting in a decrease in availability of oxygen in muscle mitochondria.²⁰

At altitude, aerobic exercise performance decreases whereas anaerobic performance potential remains stable.²⁰ For activities lasting less than a minute of high intensity, the main energy source is phosphorylation and non-oxidative production of ATP. Since quick-agility type exercises are not oxygen dependent, explosive movements are not affected by altitude.²¹

Hypoxia at altitude also can cause grave danger for the heart and lungs of an athlete. In the general circulation, hypoxia affects the vascular tone of the pulmonary and systemic vessels.⁷ There is an increase in heart rate that is related to the increase of sympathetic activity due to

resisted vessels.⁷ Bartsch⁷ states that for a given level of exercise, heart rate is greater at altitude and in order to maintain cardiac function, there is an increase in resting myocardial blood flow that is compensation for the lack of oxygen in the blood.⁷

Abnormal pulmonary function can contribute to the pathogenesis of systemic sickle cell formation.²² When lung function becomes abnormal, there is a disturbance of gas exchange that could worsen arterial hypoxemia and further promote formation of sickled cells throughout systemic circulation. It was also found that the rise in pulmonary vascular resistance was greatest at the highest altitude.²³ Even though few studies have looked at the pulmonary function of those with SCT, there have been documentations made of reductions of forced vital capacity, and arterial oxyhemoglobin saturation.²²

Pulse oximetry is a monitoring technique in order to estimate the peripheral oxygen saturation (SpO₂) of hemoglobin.²⁴ This means of intervention is able to detect levels of hypoxemia, which is defined as insufficient oxygenation of arterial blood.²⁵ A normal reading for arterial oxygen saturation is 95-100%. In a study performed by Tannheimer²⁶, he examined a group of mountaineers' oxygen saturations at altitude during maximal exertion, at rest, and during sleep. He found that their lowest oxygen saturation of 77.5% was during maximal exertion at an altitude of 4800m, suggesting a high level of oxygen depletion in a healthy individual.²⁶

VO₂ max is defined as the body's maximal ability to extract oxygen from the air and deliver it to the tissues.¹⁹ The Fick Principle states that increases of hemoglobin and/or cardiac output could contribute to the maintenance of VO₂ when saturated oxygen is reduced at altitude.²⁰ An increase in hemoglobin paired with increases in cardiac output occur in hypoxia due to sympatho-androgenic activation.²⁰ VO₂ max is dependent on the amount of hemoglobin in

the cells under normal oxygenated situations. However, a change of 1g of hemoglobin corresponds to a VO_2 change of about 3mL/min.²⁷ Previous studies have shown that an individual's VO_2 max can decrease 1.5-3.5% for every 300m of additional altitude gained over 1500m.²⁰

Hypoxia will also trigger the increase of arterial ventilation through the carotid chemoreceptors, and can sometimes compensate for the lack of partial pressure of inspired oxygen (PiO_2).²⁸ When the muscles are forced to work anaerobically, this leads to the formation of lactic acid and hydrogen ions, and a build-up of these ions can then result in defective muscle contractile function which, consequently, can impair an individual's ability to continue participating in exercise.²⁸ Other adverse health effects also occur at altitude, such as increased blood pressure and heart rate, most likely because of the increased sympathetic nervous system activity.²³

The sickled red blood cells will not be observable at rest in the peripheral blood flow, however, at high altitudes, sickling may be increased up to 9% of erythrocytes.⁴ As exercise stress and hypoxemia increase, SCT athletes can accumulate these abnormal cells in their arterial blood flow. If this happens, the cells cause an impedance of circulation and can rob vital organs of blood and nutrients.³ In one study, a military recruit with SCT cycled at high altitude, resulting in an eventual 28% of sickled cells in venous blood from the forearm.³ In situations with low oxygen levels, cells will become dehydrated and lose ions. Both of these losses can lead to an increase in intracellular hemoglobin concentration, which enhances polymerization of the red blood cells.²⁹

Between 1970 and 2003, Eichner identified 30 cases of death that were associated with severe exercise.¹⁵ Military recruits, high school and college athletes, and even athletes as young

as 12 years old participating in youth football have been identified.³⁰ It has been said that the higher intensity of the athlete, the earlier and greater the sickling.³ In order for medical professionals to be prepared for these sickling crises, we must first be able to identify at what specific climate changes are most detrimental to their health.

CHAPTER 3

METHODOLOGY

Study Design

This single blind quantitative study was designed to further understand the effects of sickle cell trait when these predisposed athletes are training at altitudes.

Subjects

Two female collegiate athletes volunteered for this study. The two participants (average of 21 ± 0 years, height: 184.15 ± 5.38 cm, 74.84 ± 9.62 kg and BMI of 22 ± 1.56) were on the volleyball and women's basketball teams. Prior to medical clearance for sports participation, each athlete underwent a blood test to identify athletes with sickle cell trait. Each athlete who participated had a documented positive result on this test, and were medically cleared to play their respective sports by the head team physician. After approval by the IRB (Protocol Number: [862124-6]) and prior to participation, each subject signed an informed consent form for the protection of human subjects.

Instrumentation

Subjects wore the Hypoxico altitude training mask, which altered the oxygenation state during the exertion test. The simulated altitudes used to test hemoglobin sensitivity were chosen in a random order, but incorporated heights of 2,470, 5,000 and 8,370 feet.

Hypoxico Altitude Training System: Serial Number: CBB1014340118

New York, NY USA

Pulse Oximetry Monitor: Oximeter Plus Oxi-Go, Serial Number: 113331501169

Roslyn Heights, NY USA

Treadmill: Landice, model L7, Serial Number: L7-101108

Randolph, NJ USA

Procedures

Prior to each subject's first trial day, they were evaluated to find their preferred running speed. The subjects were placed on a treadmill and blinded to the speed display while still allowing them to manipulate the speed controls. The subject was given the verbal command of choosing a pace that they could complete a 30-minute run. Once they found this speed, they returned the treadmill to the stop position. This was done three times, and an average of their three speeds was used for each subject's individual trials at altitude.

Within the blood, hemoglobin, percent hemoglobin S, and hematocrit was evaluated at rest and after exertion. Normal hemoglobin levels for a non-pregnant female ranges between 120-160 g/L.²⁹ Hematocrit is a ratio measure of the blood which corresponds to the volume of red blood cells compared to the total blood volume, has a normal range between 36-48% in females.³¹ The hemoglobin electrophoresis evaluated the percentage of hemoglobin S in the subject's blood. Normal values of oxygen saturation in the blood, evaluated by pulse oximetry, is between 95-100%.³²

A venous blood draw was taken from each subject before and immediately following each trial. Proper phlebotomy procedures were followed.

Protocol

During this case study, both subjects underwent three trials of the procedure, and each trial was separated with two days in between in order to replenish oxygen stores.⁸ Prior to each

trial, subjects' blood was drawn by venous blood draw for a complete blood count in order to check hemoglobin levels at rest. Immediately following the blood draw, the subject performed a 30-minute treadmill exertion test, running at their self-selected speed. Each subject wore the Hypoxico altitude simulating mask in order to change the oxygenated environments found at higher altitudes. A pulse oximetry monitor was used in order to monitor oxygen saturation. The probe was placed on the subject's finger and is able to detect the amount of oxygen traveling to the most distal extremities.³⁰ The three altitudes used to test the hemoglobin sensitivity were 2,470, 5,000 and 8,370 feet, in order to assess the individual's hemoglobin sensitivity at various oxygenation levels. Immediately following each trial, another venous blood draw took place in order to monitor the changes in the hemoglobin, as well as hematocrit, plasma enzymes, and essential clotting factors. After the second blood test was collected, subjects were monitored by a supervising physician to ensure proper replenishment of oxygen and overall health and wellbeing.

Safety

For each trial, essential safety measures for a sickling crisis were taken. There was a physician present for all trials in order to properly recognize and treat a sickling crisis if needed. In the event of a full body cramping episode, there was an ice immersion tank and an oxygen tank on site. If a cardiac emergency arose, there was an automated external defibrillator (AED) present. The pulse oximetry probe was also used for safety purposes, to track their need for extra oxygen. If the oxygen saturation value fell below 95%, it was deemed hypoxemia, and extra caution was taken for the remainder of the trial. Excessive caution and action is taken when the percentage falls below 90, which becomes a medical emergency for the subject. The signs and

symptoms of a sickling crisis were posted around the testing facility in order for the research team to recognize a possible emergency. The most common symptom of a sickling crisis is increasing pain and weakness in the working muscles, most commonly the legs, buttocks and/or low back. Rapid/difficulty breathing, confusion, and restlessness are signs of poor oxygenation.³¹

Chapter 4

Results

Two subjects who were identified with sickle cell trait during mandatory NCAA screening completed all three trials in this study. One subject was only able to complete one trial because of failures in blood draws. Data for the two subjects for all three trials, as well as the partial completion of trials for the third subject, are presented.

Subjects self-selected running speeds for moderate intensity exercise trials at simulated altitudes are shown in Table 1.

Table 1:

Subject	753 meters (2,470 feet)	1524 meters (5,000 feet)	2551 meters (8,370 feet)	Average Speed
1	1.79 m/s	1.74 m/s	1.79 m/s	1.74 m/s
2	2.01 m/s	1.88 m/s	2.06 m/s	1.97 m/s
3	1.97 m/s	2.37 m/s	2.59 m/s	2.32 m/s

Hematocrit, total hemoglobin and percent hemoglobin S did not change as a result of 30 minutes of exercise at any of the simulated altitudes for either of the subjects (Table 2).

Table 2: Hematocrit, Total Hemoglobin and Hemoglobin S

Alt (m)	Subject 1				Subject 2		
		Hct %	Total Hb g/dl	Hb S %	Hct %	Total Hb g/dl	Hb S %
753	Pre	43.2	14.1	38.5	34.4	11.6	38.4
	Post	44.7	14.6	38.4	34.8	11.7	38.7
1524	Pre	*	*	38.6	34.6	11.2	38.3
	Post	45.9	15.1	38.3	37.3	12.2	38.3
2551	Pre	43.6	14.8	38.8	34.4	11.6	38.6
	Post	45.1	15.3	38.8	36.3	12.2	38.4

* Sample clotting prevented measurement of these values.

Alt (m)	Subject 3			
		Hct %	Total Hb g/dl	Hb S %
753	Pre	*	*	*
	Post	*	*	*
1524	Pre	40.4	14.0	40.3
	Post	42.3	14.3	40.1
2551	Pre	*	*	*
	Post	*	*	*

*: trials not performed due to inability to draw blood

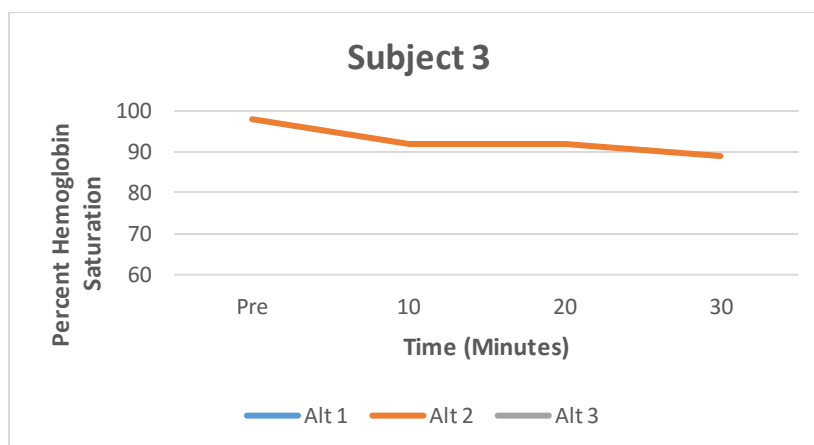
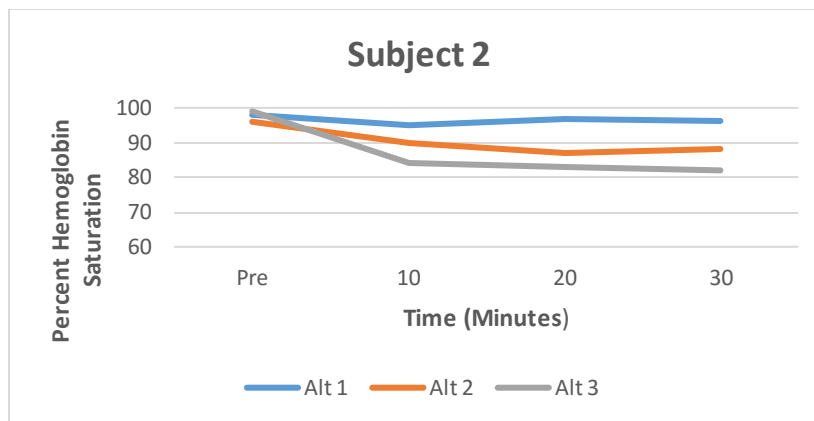
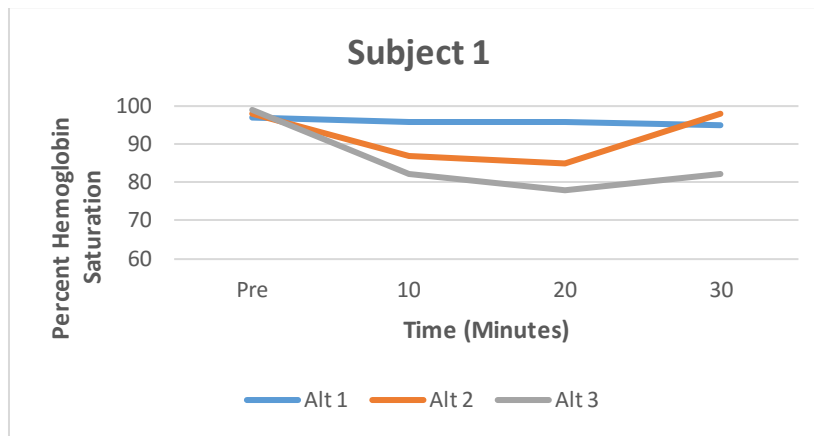
Hemoglobin O₂ saturation was determined by pulse oximetry before and at 10, 20, and 30 minutes of exercise at each altitude (Table 3). O₂ saturation did not change at the lowest altitude in either subject (Figure 1). At 5,000 feet, there was a slight decrease in saturation which persisted throughout in subject 2 and recovered to baseline in subject 1. In neither case was desaturation problematic. At the highest altitude (8,370 feet), substantial hemoglobin desaturation occurred with no indication of a return to baseline as exercise continued. Despite a severe decrease in O₂ saturation during exercise at the highest altitude, hemoglobin saturation returned to baseline levels after 3-5 minutes of recovery with rehydration.

Table 3: Oxygen saturation percent as determined by pulse oximetry

Subject 1				Subject 2			
Time	753 m	1524 m	2551m	Time	753 m	1524 m	2551m
Pre	97%	98%	99%	Pre	98%	96%	99%
10 min	96%	87%	82%	10 min	95%	90%	84%
20 min	96%	85%	78%	20 min	97%	87%	83%
30 min	95%	98%	76%	30 min	96%	88%	82%

Subject 3			
Time	753m	1524m	2551m
Pre	-	98%	-
10	-	92%	-
20	-	92%	-
30	-	89%	-

Figure 1: Hemoglobin O₂ saturation during 30-minute exercise bout at simulated altitudes



CHAPTER 5

DISCUSSION

Sickle cell trait (SCT) is a genetic condition caused by the heterozygous inheritance of a single defective globin gene.³³ A point mutation in the 6th position of the beta chain, substituting valine for glutamic acid, leads to an increase in hemoglobin S (HbS), sickled hemoglobin.³³ Red blood cells that contain mostly HbS have a tendency to become stiff, crescent moon shaped when stressed, and, as a result, can have difficulty passing through blood vessels.⁶ As these cells become more rigid and misshapen, a blockage occurs in the vessels, preventing nutrients in the circulation from continuing to areas in need. There are four main characteristics that stimulate the sickling of these cells.³ Metabolic acidosis and hyperthermia cause a rightward shift in the oxygen dissociation curve, the Bohr Effect, which facilitates a decreased hemoglobin's affinity for oxygen. Hypoxia occurs as a result of a rapid increase in oxygen uptake by skeletal muscles, or a decrease in systemic oxygen content. Finally, dehydration of red blood cells causes a relative increase in the percentage of HbS, cells which are sickled.^{3,10}

The Bohr Effect facilitates the unloading of oxygen from the hemoglobin in the blood molecules that is passing through active muscles.⁹ Red blood cells are made up of glycolytic enzymes, as well as the enzyme diphosphoglycerate (2,3-DPG). During a bout of exercise, the activity of these enzymes is increased, specifically during exertion at higher altitudes. When 2,3-DPG binds to hemoglobin, the affinity of hemoglobin for oxygen is decreased.⁹ As oxygen is released, the concentration of deoxy hemoglobin S is increased, causing the cells to become stiff and sickled. 2,3-DPG is higher in SCT cells, increasing the potential for sickling.⁹

Barometric pressure decreases as altitude increases. At higher altitudes, the partial pressure of alveolar oxygen decreases, which corresponds to a decrease in arterial partial

pressure of oxygen, leading to tissue hypoxia.^{9,21} Red blood cells of SCT athletes may have irreversible qualities at an arterial partial pressure of about 25 mmHg, which is further elevated by a decreased pH of the blood.¹⁰

Pulmonary function is altered in athletes with sickle cell trait, and can contribute to systemic sickle cell formation.²² As lung function deteriorates, pulmonary-capillary gas exchange is affected. Arterial hypoxemia promotes sickled cells, starting on the venous side of the circulation when oxygen is unloaded from hemoglobin S. As exercise and stress increase, the sickled cells spread throughout the circulation, impeding blood flow to the heart, brain and muscles, robbing them of vital nutrients.³ Hypoxia affects the vascular tone of pulmonary and systemic vessels which causes an increase in sympathetic activity due to blocked vessels.⁷ With a lack of oxygen comes a lack of energy, forcing the muscles to work anaerobically. This process leads to the formation of lactic acid and hydrogen ions, which can cause defective muscle contractions, and inhibit the performance of prolonged exercise bouts.²⁸

Vaso-occlusive crises are recurrent with sickle cell trait during high levels of exertion.¹³ This occurs due to the obstruction of small blood vessels by the abnormally shaped sickled cells. When muscle ischemia occurs, pain occurs most commonly in highly vascularized areas such as the spine, chest and abdominal region.¹⁴ Short bursts of intense exercise can cause multiple physiological processes that could trigger the sickling of red blood cells. Decreases in both pH and plasma volume are paired with an increase in sympathetic blood flow, oxidative stress, heat production, tissue hypoxia, and the release of inflammatory mediators.³² Other conditions that may foster sickling include an increased core body temperature, increased blood viscosity, ambient heat index, and dehydration, but the role of these factors is unclear.¹⁰

In the current study, the lowest hemoglobin oxygen saturation recorded was 76% at the highest altitude of 8,370 feet, or 2,551m. In an attempt to compare this value to an individual without SCT, we must look at other studies performed due the inability to use a control subject. Referring back to a study performed on mountaineers that recorded their oxygen saturations at maximal exertional, at rest and during sleep,²⁶ their lowest value was 76.5% during maximal exertion at an altitude of 4,880m. Thus, the hemoglobin saturation of the SCT athletes in the current study was the same as the mountaineers at half the altitude, suggesting that the SCT athlete is more sensitive to losing their oxygen molecules than those individuals without the SCT condition.

In a similar study by A.S. Bowers et al,³⁴ optimal hematocrit levels for females and males with both sickle cell trait and sickle cell disease were determined. Depending on the severity of the anemia of the individual, a normal hematocrit value for a woman with SCT ranges between 35-40%. The authors concluded that females with SCT need an additional 4% increase in hematocrit to match non SCT women. In the current study, hematocrit in all but one trial of one of the subjects was below the optimal hematocrit level for females with SCT. Bowers also suggested that if the hematocrit level is too high, there are increased viscous properties due to increased cell volume.³⁴ In contrast, if the hematocrit level falls too low, the oxygen carrying capacity of the blood is impaired (anemia). A lower than optimal hematocrit level over a long period of time, could indicate an increase in aerobic capacity due to heat acclimation, or an increase of plasma volume.³⁴ Hematocrit changes with systemic dehydration, which occurs with hyperventilation at altitude. These changes could explain the altered hematocrit observed at the higher altitudes in the current study.

The normal level of Hemoglobin S in the SCT athlete ranges from 35 to 45% of total hemoglobin.¹⁷ The risk of a sickling crisis within the low to high range of hemoglobin S is unknown. However, one can assume that the individual with a higher percentage of hemoglobin S, even within the normal range, may be predisposed to greater risk of sickling, especially during times of dehydration or hypoxemia. Conversely, athletes with percent hemoglobin S at the lower end of the normal range may be at relatively low risk and thus able to exercise somewhat more vigorously than those at the higher end.

The aim of this study was to determine changes in blood in athletes with (SCT due to exercise at simulated altitudes. Contrary to our hypothesis, there were no unusual changes in the amount of hemoglobin, hematocrit, or percentage of hemoglobin S at different altitudes compared with rest, and no sickling crises occurred as a result of the exercise. In fact, the amount of hemoglobin in the blood seemed to be the least varying factor for the majority of the trials. Perhaps, the longer these athletes are running at a mild to moderate pace, their cells adapt to the change in the oxygen environment in order to keep them not only moving, but moving safely. The percent hemoglobin oxygen saturation returned to within 1% of the pre-test level, suggesting the possibility of adjustment to steady state exercise. Although the speed for each subject may not have been sufficient enough to cause oxidative stress, this may have clinical significance. In order to obtain the same conditioning effects as non-SCT athletes, other methods may need to be employed. Rather than implementing harder and faster sprints and shuttle runs, exercises that may exacerbate the SCT condition, perhaps the optimal way to achieve ideal aerobic capacity is mild intensity exercise over both an extended period of time in a single bout of exercise, as well as over an extended period of time to build up effects of cardiovascular benefits. In this study, trials performed at 2,470 and 5,000 feet indicated that, percent hemoglobin oxygen saturation

returned to normal at the 30-minute mark, suggesting that these athletes may need about 30 minutes to acclimate themselves and their bodies to the changed environment.

Measurement of hemoglobin oxygen saturation, as measured via pulse oximetry, indicated how long it took the athletes with SCT to acclimatize to their changed environment. In the majority of the trials, the percent hemoglobin saturation was back to within 1% of the pre-test oxygen saturation. In the few trials that had not returned to within 1% of their pre-test values, specifically those at the highest altitude, oxygen saturation was back to pre-exercise levels after about five minutes of rest and rehydration.

Although our results did not show any abnormal changes in the blood parameters measured, the results may have clinical significance. A SCT athlete at rest has a normal level of hemoglobin S that ranges from 35-45% of the total hemoglobin content.¹⁷ Instead of simply obtaining a positive or negative result for these at risk athletes, an additional direction for these tests could be to obtain the specific percentage of hemoglobin S in their blood at rest. Knowing at which end of the 35-45% of the normal spectrum the athlete falls could indicate dangerous exertion levels. Greater precautions may be necessary for an athlete on the higher end of the range, as well as allowing for a longer time for acclimation to altitude. Starting levels of hemoglobin S in all trials for all subjects were 38%, which is in the middle of the normal range for SCT, which may account for the lack of any issues during the trials.

The National Athletic Trainers' Association (NATA) has set forth guidelines for SCT athletes in order to protect them from overexertion.³ Slower increments in training intensity and longer recovery times in between bouts are recommended, as are restrictions on timed runs or any kind of all out exertion for 2-3 minutes with no recovery time. Other recommendations

include unrestricted hydration and adjusted work cycles based on heat and any other medical conditions, such as asthma.³ These guidelines are intended to set safe exercise limits for the SCT athlete. Since ischemia occurs most commonly in highly vascularized areas, cramping in the spine, chest, and abdominal region should be taken very seriously and treated like a medical emergency.¹⁴ Symptoms of these crises typically occur with no preceding symptoms and the muscles looking and feeling like normal. Athletes experiencing a crisis will typically be unable to hold themselves up, and complain of pain in their legs and buttocks, another common area due to the bone marrow within long bones.³

Conclusions

It is important for the sports medicine team to work together in keeping the health and wellbeing of the athletes the utmost priority. In doing so, the team must educate themselves about specific conditions that may cause grave consequences to those under their care. Although there were no major variabilities in the blood measures tested in the current study, there are some relevant clinical indications. The current study concluded that the SCT athletes tested has a noticeably increased sensitivity to altered oxygenation environments, but have a tendency to adjust to the change during steady state exercise. Adequate testing before certifying eligibility to participate may provide insight into potential cellular shortcomings these individuals may experience and suggest limits on their exertion level to reduce the risks of sickling crises. Further research is necessary on SCT athletes at altitudes and various environmental conditions in order to properly care for them.

APPENDIX A: IRB MATERIALS



**UNLV Biomedical IRB - Expedited Review
Approval Notice**

DATE: April 18, 2016

TO: John Young, PhD
FROM: UNLV Biomedical IRB

PROTOCOL TITLE: [862124-6] The Effects of Altitude in Athletes with Sickle Cell Trait
SUBMISSION TYPE: Revision

ACTION: APPROVED
APPROVAL DATE: April 18, 2016
EXPIRATION DATE: April 17, 2017
REVIEW TYPE: Expedited Review

Thank you for submission of Revision materials for this protocol. The UNLV Biomedical IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a protocol design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

PLEASE NOTE:

Upon approval, the research team is responsible for conducting the research as stated in the protocol most recently reviewed and approved by the IRB, which shall include using the most recently submitted Informed Consent/Assent forms and recruitment materials. The official versions of these forms are indicated by footer which contains approval and expiration dates.

Should there be *any* change to the protocol, it will be necessary to submit a **Modification Form** through ORI - Human Subjects. No changes may be made to the existing protocol until modifications have been approved.

ALL UNANTICIPATED PROBLEMS involving risk to subjects or others and SERIOUS and UNEXPECTED adverse events must be reported promptly to this office. Please use the appropriate reporting forms for this procedure. All FDA and sponsor reporting requirements should also be followed.

All NONCOMPLIANCE issues or COMPLAINTS regarding this protocol must be reported promptly to this office.

This protocol has been determined to be a Minimal Risk protocol. Based on the risks, this protocol requires continuing review by this committee on an annual basis. Submission of the **Continuing Review Request Form** must be received with sufficient time for review and continued approval before the expiration date of April 17, 2017.



UNLV IBC

Approved

DATE: March 14, 2016

TO: John Young
FROM: UNLV IBC

PROJECT TITLE: [883491-1] The Effect of Altitude in Athletes with Sickle Cell Trait
REFERENCE #:
SUBMISSION TYPE: Revision

ACTION: APPROVED
APPROVAL DATE: March 14, 2016
EXPIRATION DATE: March 13, 2019

Thank you for your submission of Revision materials for this research project. The UNLV IBC has APPROVED your submission. All research must be conducted in accordance with this approved submission.

Please note that any revision to previously approved materials must be approved by this committee prior to initiation. Please use the appropriate amendment form for this procedure.

Please report all NON-COMPLIANCE issues regarding this project to this committee.

Renewals

All projects expire three years after the approval date. You must submit and obtain approval for a new project prior to March 13, 2019 to avoid any lapse in approval.

If you have any questions, please contact Kevin Bergeron at (702) 895-5453 or kevin.bergeron@unlv.edu. Please include your project title and reference number in all correspondence with this committee.

Office of Research Integrity - IACUC & IBC
4505 Maryland Parkway . Box 454022 . Las Vegas, Nevada 89154-4022
(702) 895-5453

APPENDIX B: MISCELLANEOUS APPROVALS



INFORMED CONSENT

Department of Kinesiology and Nutrition Sciences

TITLE OF STUDY: The Effects of Altitude in Athletes with Sickle Cell Trait

INVESTIGATOR(S): Samantha Reynolds, Dr. John Young, Dr. James Navalta, Dr. Kara (Miller) Radzak

For questions or concerns about the study, you may contact Samantha Reynolds at (609) 682-0284, Dr. John Young at (702) 895-4626, Dr. James Navalta at (702) 895-2344.

For questions regarding the rights of research subjects, any complaints or comments regarding the manner in which the study is being conducted, contact **the UNLV Office of Research Integrity – Human Subjects at 702-895-2794, toll free at 877-895-2794 or via email at IRB@unlv.edu.**

Purpose of the Study

Individuals who have inherited the sickle cell trait gene may experience some symptoms as they exert themselves during exercise, especially at higher altitudes. The purpose of this study is to evaluate the sensitivity of athletes with a diagnosed sickle cell trait to moderate intensity exercise at various altitudes by examining differences in your blood profile.

Participants

Participants in this study must be healthy collegiate athletes who have been diagnosed as having the sickle cell trait as a result of NCAA mandated screening.

Dr. Rosenberg, Director, UNLV Sports Medicine Department, has given his approval for your participation in this study, should you choose to participate.

Procedures

If you volunteer to participate in this study, after giving informed consent, you will be asked to do the following: You will be asked to come to the Exercise Physiology laboratory (MPE 326) where you will complete a total of 3 trials. Each trial will consist of a 30 minute moderate intensity treadmill run at your self-selected preferred speed. There will be a minimum of 2 days between each trial. While performing these trials, you will be wearing an altitude simulating face mask which will change the atmosphere to lower oxygen levels representing 3 different altitudes, in a randomized order. A pulse oximeter will be worn on your finger to monitor the levels of oxygen saturation. Before and after each trial a blood sample (about a tablespoon) will be taken from a vein in your arm by venipuncture by a qualified member of the research team for the determination of total blood count, hemoglobin, hematocrit, and the percentage of sickled cells. These measurements will be done by a commercial laboratory and will be the only things measured in your blood. After the second blood draw, you will be monitored by a supervising physician to ensure proper oxygen replenishment and overall well-being before being released from the laboratory.

Benefits of Participation

The direct benefit to you for participating is to gain a better understanding of how you respond to exercise at different altitudes and how your sickle cell trait gene may affect your athletic performance.



January 28, 2016

To Whom It May Concern,

I am writing to express my support in the thesis project of Samantha Reynolds entitled "The Effects of Altitude in Athletes with Sickle Cell Trait". As the head team physician at the University of Nevada- Las Vegas, I agree to the terms of this study, and I will provide physician oversight for all trials to ensure all subjects' health and wellbeing during the testing procedure. If you have any questions or problems, please do not hesitate to contact me at (702) 895-4033.

A handwritten signature in black ink, which appears to read "William Rosenberg, M.D.", is written above the printed name.

William Rosenberg, M.D.
University of Nevada- Las Vegas
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