HEART RATE VARIABILITY COMPARED IN A TRAINED AND UNTRAINED POPULATION UNDER NORMOXIC AND HYPOXIC CONDITIONS

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by

Shannon L. Wilson

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Department of Kinesiology

Abstract

of

HEART RATE VARIABILITY IN A TRAINED AND UNTRAINED POPULATION UNDER NORMOXIC AND HYPOXIC CONDITIONS

by

Shannon L. Wilson

Introduction

Heart Rate Variability (Atlaoui et al.) is greater in aerobically trained athletes due to an increase in parasympathetic tone. While high levels of aerobic training are generally associated with good cardiovascular responsiveness, it sometimes leads to suppressed responsiveness.

Purpose

To examine the cardiovascular and autonomic changes that occur in trained and untrained subjects exposed to hypoxic (H) and normoxic (N) conditions.

Methods

Seven aerobically trained men (6 trained cyclists, 1 runner; age: 29.14 $\pm$ 4.37 yrs, height: 72.1 $\pm$ 2.1 in, weight: 77.9 $\pm$ 7.2 kg, average training hours/week 14.6 $\pm$ 4.35) and 6 untrained men (age: 28.3 $\pm$ 4.8 yrs, height: 69.41 $\pm$ 3.0 in, weight 81.43 $\pm$ 16.9 kg) were recruited for this study. This study used a double-blind crossover design and subjects were randomly assigned treatment order. Subjects rested for one hour and EKG (Hexoskin) was recorded as well as SaO_2. After one hour BP was taken. Subjects then completed a submaximal exercise bout (1.5 watts/Kg

BW) for 10 minutes. Subject then reported back to lab for a second test to receive the opposite treatment. Standard deviation of normal-to-normal interval (SDNN) was calculated for each subject during rest and exercise for each environmental treatment. HRV, BP, HR, and SaO_2 were analyzed using a Wilcoxon test of Correlated Groups and a Mann-Whitney U test for the difference between two independent samples. An alpha level of 0.05 was used for significance.

Results

Trained subjects had a trend (significant at 0.1 level) towards an ANS mediated response (N: 17.57 $\pm$ 16.6 ms, H: 8.14 $\pm$ 6.2 ms), while UT subjects did not change during exercise in different environments. Untrained subjects had a significant increase in HR during the exercise bout in hypoxia when compared to that of the normoxic bout (N: 139.2 $\pm$ 26.1bpm, H: 151.5 $\pm$ 28.4 bpm) when the trained group did not significantly differ between environments (N: 101.6 $\pm$ 23.1 bpm, H: 112.8 $\pm$ 20.9 bpm). Trained subjects had a significant increase in BP in the hypoxic bout of exercise (N: 143.3 $\pm$ 10.8 mmHg, H: 150.3 $\pm$15.8 mmHg) while the untrained subjects did not (N: 155.3 $\pm$ 9.4 mmHg, H: 159 $\pm$ 15.7 mmHg).

Conclusion

Trained subjects may be more sensitive to small changes in autonomic stimuli whereas Untrained subjects are not as sensitive to change. Both groups were found to be equally responsive to strong autonomic stimuli.

_____, Committee Chair
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_____
Date

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Chapter 1

INTRODUCTION

Regular exercise is commonly thought of as a keystone of a “healthy lifestyle” as it is key in decreasing the risk of prominent diseases such as cardiovascular disease. Many groups have been able to demonstrate that regular physical exercise stimulates beneficial physiological adaptations that have a similar effect to commonly prescribed prescription drugs (O'Keefe et al., 2012), decreasing the risk of a number of prevalent and chronic diseases such as coronary artery disease (CAD), depression, hypertension, obesity, anxiety, and type II diabetes (Haskell et al., 2007). Health professionals have suggested for many years that exercise has a dose-response relationship. This relationship has been touted by the media and practiced by society. However, little consideration is given to the idea that there may be an upper limit to this relationship.

Athletes who commonly participate in regular exercise, specifically endurance athletes, tend to have superior physiology compared to the average person (K. P. George, L. A. Wolfe, & G. W. Burggraf, 1991). Most commonly seen is the expansion of blood volume, increase in myocardial capillary density, increased tolerance to ischemia, enlarged heart, and autonomic changes that improve stress response (Lavie et al., 2015). These adaptations support the sustained and persistent volume of training at an increased workload, affecting nearly every organ system.

Nearly all aspects of vascular and cardiac control are regulated by the autonomic nervous system (ANS). Made up of sympathetic and parasympathetic branches, the autonomic nervous system is a constant alteration of input and withdrawal- fluctuating

heart rate (HR), blood pressure (Kraemer et al.), and other factors needed to support cardiac output quickly and efficiently. Evidence has shown that neural mechanisms appear to be important in mediating the initial response at the onset of exercise and stress. This includes very rapid changes in heart rate and blood pressure essential for increased cardiac output (Aubert, Seps, & Beckers, 2003). With the quick response of vagal tone (typically increased in trained individuals) cardiovascular changes in heart rate and blood pressure are able to adapt to respond to the needs of the individual (Aubert et al., 2003). Individuals with low vagal tone tend to be unable to respond rapidly, causing cardiovascular damage and leading to an increase in mortality (Almedia & Araujo, 2003). Heart rate and how it fluctuates on a beat-to-beat basis (using the R-R interval based on EKG) can be used in order to monitor autonomic influx and withdrawal.

Heart Rate Variability (HRV) was first documented by Stephen Hales in the early 18th century when he first reported fluctuations in beats as well as arterial pressure, leading him to believe that these fluctuations coincided with respiratory cycles (Billman, 2011). Since this first discovery, both time and frequency analysis techniques have to been used to interpret the sympathetic and parasympathetic inputs. Through this analysis, Francis D. Donders suggested that the changes in heart rate and the variations beat-to-beat were due to an increased influence of parasympathetic input from the vagus nerve (Billman, 2011).

With these small beat-to-beat changes and increase in parasympathetic input, it allows for the body to make small adjustments needed to respond appropriately to physiological stimuli. Therefore, autonomic function may be protective with factors in

chronic disease. However, high volumes of physical activity and physiological stimuli, such as that commonly seen in endurance athletes, may create too much parasympathetic input and consequently decrease the protective nature of the ability of the cardiovascular system to respond.

In two notable articles published in 2013 were able to demonstrate this phenomenon. Doutreleau et al., (2013) showed a case study of two master's level triathletes developing type 2, second degree AV blocks that onset with exercise. Hypothesized to be caused from increase in parasympathetic tone that cannot be overcome by the sympathetic system, Doutrelelau et al. demonstrated what had been discussed by Grundvold et al., (2013) in an article published months prior. Grundvold and colleagues completed a follow up study with over 2000 men in Norway from a prior study in 1972-1975. After the 30-year follow up, 13% of subjects developed atrial fibrillation, and found that subjects whose heart rate did not surpass 100 bpm on submaximal exercise bouts had the highest incidence of developing atrial fibrillation later on in life (Grundvold et al., 2013). This blunted heart rate (typically thought to be caused by increased parasympathetic tone) may not actually be a protective mechanism.

Hood and Northcote (1999) demonstrated that an increase in parasympathetic tone can in fact be detrimental. In a 12-year follow up study, 19 veteran endurance athletes were followed. Fifty-eight percent of subjects had stage 1 hypertension, 32% of subjects had first-degree AV blocks, and 100% of subjects demonstrated bradycardia. After 12 years, subjects were placed on a holter monitor where 53% of subjects demonstrated bradycardia throughout the day. Ninety- five percent of subjects had ventricular ectopy

ranging from 5- 10,931 ectopic beats in a 24-hour period. Two of the 18 subjects required pacemakers for 2nd and 3rd degree AV blocks. This data suggests that highly trained endurance athletes may not be able to respond to cardiovascular stress as well as lesser-trained subjects and that an upper limit to the benefits of training may exist.

Purpose

To examine the cardiovascular and autonomic changes that occur in a trained population vs an untrained population when exposed to physiological stress and differing environmental conditions.

Significance of the Study

As the studies discussed prior show, the benefits of cardiovascular fitness may have an upper limit. Those who may have been thought to have superior cardiovascular fitness, may not adapt as well as we think to small and large physiological stress. Hypothetically, it has been believed that the more parasympathetic tone one has, the better the person can adapt to small and large stresses. Previous data questions that hypothesis and there is a large gap in the literature on how well subjects are able to adapt to small and large stresses in comparison with training status.

Hypotheses

1. Trained subjects will not have a significant decrease in SDNN at rest under hypoxic conditions.
2. Trained subjects will not have a significant decrease in SDNN at rest under normoxic conditions.

3. Trained subjects will not have a significant decrease in SDNN during submaximal exercise under hypoxic conditions.
4. Trained subjects will not have a significant decrease in SDNN during submaximal exercise under normoxic conditions.
5. Untrained subjects will not have a significant decrease in SDNN at rest under hypoxic conditions.
6. Untrained subjects will not have a significant decrease in SDNN at rest under normoxic conditions .
7. Untrained subjects will not have a significant decrease in SDNN during submaximal exercise under hypoxic conditions.
8. Untrained subjects will not have a significant decrease in SDNN during submaximal exercise under normoxic conditions.
9. Trained subjects will not have a significant decrease in SaO_2 at rest under hypoxic conditions.
10. Trained subjects will not have a significant decrease in SaO_2 at rest under normoxic conditions.
11. Trained subjects will not have a significant decrease in SaO_2 during submaximal exercise under normoxic conditions.
12. Trained subjects will not have a significant decrease in SaO_2 during submaximal exercise under hypoxic conditions.
13. Untrained subjects will not have a significant decrease in SaO_2 at rest under hypoxic conditions.

14. Untrained subjects will not have a significant decrease in SaO_2 at rest under normoxic conditions.
15. Untrained subjects will not have a significant decrease in SaO_2 during submaximal exercise under hypoxic conditions.
16. Untrained subjects will not have a significant decrease in SaO_2 during submaximal exercise under normoxic conditions.
17. Trained subjects will not have a significant increase in HR at rest under hypoxic conditions.
18. Trained subjects will not have a significant increase in HR at rest under normoxic conditions.
19. Trained subjects will not have a significant increase in HR during submaximal exercise under hypoxic conditions.
20. Trained subjects will not have a significant increase in HR during submaximal exercise under normoxic conditions.
21. Untrained subjects will not have a significant increase in HR during rest under hypoxic conditions.
22. Untrained subjects will not have a significant increase in HR during rest under normoxic conditions.
23. Untrained subjects will not have a significant increase in HR during submaximal exercise under hypoxic conditions.
24. Untrained subjects will not have a significant increase in HR during submaximal exercise under normoxic conditions.

25. Trained subjects will not have a significant increase in systolic blood pressure (SBP) at rest under hypoxic conditions.
26. Trained subjects will not have a significant increase in SBP at rest under normoxic conditions.
27. Trained subjects will not have significant increase in SBP during submaximal exercise under hypoxic conditions.
28. Trained subjects will not have a significant increase in SBP during submaximal exercise under normoxic conditions.
29. Untrained subjects will not have a significant increase in SBP at rest under hypoxic conditions.
30. Untrained subjects will not have a significant increase in SBP at rest under normoxic conditions.
31. Untrained subjects will not have a significant increase in SBP during submaximal exercise under hypoxic conditions.
32. Untrained subjects will not have a significant increase in SBP during submaximal exercise under normoxic conditions.

Definition of Terms

bpm: beats per minute (unit of heat rate).

HR: heart rate- the number of heart beats per minute if rate was maintained.

HRV: heart rate variability- the variability in the distance between the R-R intervals on an EKG.

Hypoxia: A lower than normal amount of oxygen (20%) in outside environment.

Normoxia: Normal amount of oxygen (20%) in room air.

SaO_2: Oxygen saturation of arterial blood

SBP: Systolic blood pressure- the pressure in the arteries when the left ventricle contract.

SDNN: Standard Deviation of normal-to-normal beats- Standard deviation of R-R intervals.

SV: Stroke Volume- The volume of blood pumped out of the heart with each contraction.

Chapter 2

REVIEW OF LITERATURE

The current thought on exercise is: the more the better. This logic is even supported by the majority of literature and even the American College of Sports Medicine (ACSM). ACSM currently recommends ≥ 150 minutes of moderate aerobic exercise, or ≥ 75 min at a vigorous intensity (*American College of Sports Medicine Guidelines for Exercise Testing and Prescription*, 2013). While much of the literature supports the health benefits of exercise, some argue that extreme endurance exercise can counter the beneficial aspects of exercise (O'Keefe & Lavie, 2013). It has been argued that humans are not genetically adapted for the type of sustained, extreme aerobic efforts that endurance athletes put themselves through (Patil et al., 2012) and long term endurance exercise may be detrimental towards cardiovascular health.

The Dose-Response Relationship of Exercise

The prevailing logic in our modern day society is that there is a linear dose-response relationship between exercise and health. While as little as 15 minutes of daily physical activity have been shown to significantly reduce the risk of chronic diseases, some researchers have questioned whether the more exercise one person does, the more health benefits that are gained. Wen et al., (2011) was able to demonstrate, using over 400.000 individuals, that past a minimum of 15 minutes of exercise per day, every additional 15 minutes of exercise decreased all cause mortality by 4% in a step-wise fashion. Lee et al., (2012) completed a 15-year observational study, finding that the dose-response relationship was indeed U-shaped for all cause mortality. Those who exercised

at a higher speed, distance, and frequency, had an increased risk for chronic diseases and ultimately death. Other studies have shown an increased risk in coronary artery disease in endurance athletes. Schwartz, Merkel-Kraus, and Duval (2010) found long-term marathon runners had significantly more plaque volume when compared to sedentary controls. This finding was similar to Breuckmann et al. (2009) in which the authors examined a group of long term marathoners, finding that they had 60% more plaque when compared to age-matched controls.

With more and more life-long athletes being diagnosed with dangerous cardiac arrhythmias and other issues, this U-shaped dose-response relationship curve needs to be further examined. Commonly compared to a pharmaceutical drug, an insufficient amount of exercise will not grant the beneficial adaptations needed for health and disease prevention, while too much can cause harm (O'Keefe & Lavie, 2013). Lee, Patte, Lavie, and Blair (2012) were able to demonstrate that subjects who ran between 6-7 mph, 1-20 miles per week, 2-5 times per week were deemed at optimal peak to reap the benefits from exercise. Those who increased any variable past that showed a decrease in benefit and adaptation.

Not all exercise may cause this extent of damage to the body. Light to moderate exercise has not been shown to implement the dose-dependent risks that are commonly seen with vigorous, long-term endurance exercise (O'Keefe & Lavie, 2013). This presents an interesting argument for a fitness community so intent on high intensity interval training. Exercise should certainly not be discouraged or viewed as harmful, but should be carefully examined and prescribed just like any medication.

Health Benefits of Exercise

Exercise has been shown to have many different health benefits and it one of the most underused therapies by prescribing medical practitioners. Research has provided a multitude of evidence; demonstrating that exercise can reduce the risk of cardiovascular disease, type II diabetes mellitus, stroke, depression, and even prevent Alzheimer's (Patil et al., 2012). Research has repeatedly shown that aerobic exercise typically instigates positive physiological adaptations.

Differences and changes that occur in the heart of athletes was first documented in 1898 by Henschen et al. (K. George, L. A. Wolfe, & G. Burggraf, 1991) in which what was found was alarmingly similar to features of a diseased heart. The term "athlete's heart syndrome" first appeared in the 1960's to describe these structural and physiological changes and was coined a "diseased state" (Gott, Roselle, & Crampton, 1968). Symptoms of athletic heart syndrome include; bradycardia, heart block (1rst, 2nd, and 3rd degree), ST segment changes, third and fourth heart sounds, and cardiac enlargement (K. P. George et al., 1991). It wasn't until recently that scientists have begun to believe that these changes can be beneficial and positive adaptations to the heart (Crisafulli et al., 2002) which is still a hotly debated topic to this day.

Resting Bradycardia is one of the most common finding in male endurance athletes (Ekblom, Kilbom, & Soltysiak, 1973; Underwood & Schwade, 1977; Zoneraich, Rhee, Zoneraich, Jordan, & Appel, 1977) appearing in nearly 75% of endurance athletes and 20% of sprinters (K. George et al., 1991). While bradycardia is sometimes quite serious, the increase thickness of the ventricles as well as cardiac enlargement allows for

athletes to increase stroke volume while still decreasing heart rate maintain or even surpass needed cardiac output (K. George et al., 1991). A much more metabolically efficient method, a lower heart rate allows for a longer diastole and a larger stroke volume with each beat (Kiviniemi, Tulppo, Hautala, Vanninen, & Uusitalo, 2014).

Ekblom et al. (1973) were the first to provide evidence that this decrease in resting heart rate may be due the increase in parasympathetic tone and a decrease in sympathetic tone influences endurance athletes. While slowing heart rate, the increase in parasympathetic tone allows for the body to make necessary minute adjustments required to adapt to stress and stimuli as well as act as an antiarrhythmic, protecting the body from chronic stress and dangerous arrhythmias (Kiviniemi et al. (2014).

Autonomic Adaptations to Exercise

The cardiovascular system is mainly controlled by central command through the brainstem, sympathetic, and parasympathetic nervous systems, though it can also be mediated by baroreceptors, catecholamine's, chemoreceptors, and tissue metabolism (Aubert et al., 2003). A constant flux of parasympathetic and sympathetic input, each system fluxes and reduces inversely to the other to provide constant input to the cardiovascular system. The parasympathetic nervous system (innervated by the vagus nerve) has a nearly instantaneous response, and is responsible for the beat-to-beat fluctuations in heart rate (HRV), blood pressure, and stroke volume. This near constant input allows the cardiovascular system to properly adjust to the environment and any physiological stress (Kiviniemi et al., 2014).

Exercise and training has been shown to improve parasympathetic tone (Aubert et al., 2003; Kiviniemi et al., 2014). Lower resting heart rate and bradycardia in athletes has been shown to be directly linked to an increase in parasympathetic tone (Schmitt et al., 2008) and even been associated with an improvement in endurance exercise (Schmitt et al., 2006). Marcor et al. (1996) examined 10 cyclists and found that in compared to controls, the cyclists had an enhanced parasympathetic drive to the sinus node. In 2002 Stien et al. conducted a pharmacological blockade study, using atropine (block parasympathetic) and propranolol (potent beta-blocker). The authors found that sensitivity was blunted in athletes in comparison to that of non-athletes. They concluded that training may induce intrinsic adaptations in conduction velocity, which contributes to the increased prevalence of AV abnormalities observed by athletes. Conversely, Katona et al., disagreed entirely. They provided evidence that stated that decreases in resting heart rate were solely due to a reduction in intrinsic cardiac rate, not an increase in parasympathetic tone. While there is some discrepancy in the research on why heart rate is lowered, there is substantial evidence that there is an increase in parasympathetic tone with training.

Heart Rate Variability as a Marker for Autonomic Input

Heart rate variability (or the variability in the R-R interval with each beat) is a commonly used, non-invasive technique to monitor and measure autonomic input to the heart. Most commonly taken from a 24 hour holter monitor, incidences of heart rate variability (HRV) can be measured for 24 hours, or more commonly, 5 minute segments ("Heart Rate Varoiability: Standards of measurement, physiological interpretation, and

clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996). As an affordable, non-invasive, yet indirect technique, it is commonly used in research as a "gold-standard" technique for autonomic modulation (Bernardi et al., 1998). With the mystery of cardiac sudden death and an increase incidence in harmful and lethal arrhythmias on the rise, HRV has risen as a promising marker as it allows indirect measurements of parasympathetic and sympathetic input ("Heart Rate Varoiability: Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996). In 1996, European and North American task force gathered and compiled research to set HRV as a standard measurement. The guidelines and standards set by this task force give more validity and standardization to research practices utilizing HRV measures.

Cardiovascular Abnormalities in Endurance Athletes

With many different studies and across the last few decades, it has been established that chronic and high intensity endurance exercise training have an effect of both structural and electrical adaptations of the heart. Though these elite and chronic training athletes may be young, over time, they have been shown to see symptoms that are beginning to effect lifestyle, training, and are not considered benign. A 12-year follow up study by Hood and Northcote (1999) found that Master's level athletes had a variety of problems when they continued training at high levels over the years. Three of their 19 subjects required pacemakers and one subject had a resting heart rate of 17. They

considered these effects to be substantial, as detraining successfully treated most of the symptoms.

It appears that cardiac remodeling and increase in autonomic control induced by excessive endurance training can create rhythm abnormalities and arrhythmogenic substrates, making arrhythmias the most common cardiovascular problem veteran athletes encounter (Ector et al., 2007; Goel et al., 2007; Mohlenkamp et al., 2008). Therefore, it has been stated by many that chronic endurance training should be considered a risk factor for the most common arrhythmias that athletes experience, such as atrial fibrillation and atrial flutter (Doutreleau et al., 2013). Sorotin et al., (2011) published a meta-analysis of atrial fibrillation in endurance athletes, reporting that there is an increase in atrial size, inflammation (marked by C-reactive protein), a decrease in sympathetic tone, with an increase in parasympathetic tone. Karjalainen et al., (1998) provided evidence that long term vigorous exercise (3 hrs per week for the last 2 years) is associated with an increased likelihood of atrial fibrillation in middle-aged men. The authors also found that out of the people who developed atrial fibrillation, 62.7% of them were defined as athletes. A later study by Aizer et al. (2009) showed that long-term endurance exercise provided a 20% increase in incidence of atrial fibrillation.

How much exercise is too much, though? Elosua et al. (2005) showed that more than 1500 lifetime hours of ‘intense’ exercise was associated with a three times higher prevalence of lone atrial fibrillation and a five times higher prevalence of vagal lone atrial fibrillation. If medical and fitness professionals are prescribing more and more exercise,

it is only ethical to investigate this upper limit to exercise as well as the U-shaped dose-dependent curve.

Rationale

It is evident that endurance exercise and training stimulates many physiological and structural changes within the human body. Some adaptations are beneficial up to a certain, currently undefined point. While there is a need to delve further into a defined point on the dose-dependent curve, the question still remains: are these adaptations really beneficial?

Several authors have argued this point, yet the evidence is still not conclusive. The adaptations and symptoms of athletic heart syndrome mimics disease, yet functionally are different. The increase in parasympathetic tone with training has led researchers to question if this really is a protective mechanism by the body. Prior investigations have looked at adjustments made under a variety of different stressors such as hypoxia (Bernardi, Passino, Serebrovskaya, Serebrovskaya, & Appenzeller, 2001; Bernardi et al., 1998) and exercise (Da Silva, Verri, Nakamura, & Machado, 2014). While hypoxia and environmental changes are a smaller stress on the autonomic system, exercise and increase in activity remain a much larger stress, stimulating a higher and quicker autonomic response. There is currently a gap in the literature involving the comparison of trained individuals and untrained individuals and how they respond physiologically to differing levels of stress.

Chapter 3

METHODS

Participants

Seven trained and six untrained men (ages 18-45) were recruited from the Sacramento Area for this study. All subjects were recruited by word of mouth. Descriptive characteristics can be viewed in Table 1. Trained subjects were required to be currently training for an endurance sporting event (i.e running or cycling), as well as training >8 hours per week on average for the last two years, and actively competing in races. Untrained subjects were required to exercise 3 times or less per week on average for the last 3 months.

Subject 6 and 10 were omitted from final data. Subject 6 dropped out of the study due to scheduling conflict. Subject 10 completed the study, but due to the double blind nature of the study, researcher's failed to note discrepancies in the EKG, and therefore all data could not be accurately recorded.

Health History and Screening

Prior to testing, all subjects were asked to complete an adapted version of the American Heart Association (AHA) and American College of Sports Medicine (ACSM) health screen (*American College of Sports Medicine Guidelines for Exercise Testing and Prescription*, 2013). Health questionnaire is included in appendix 1. Subjects that were screened as high risk for cardiovascular disease and sudden cardiac death were excluded. Of the subjects that were considered for this study, none had to be excluded because of health risk.

Training and Diet Recall

Subjects were asked to recall an approximation of their training and exercise from the week prior. They were asked to list exercise type, length, and rate of perceived exertion (via a 10 point scale) and asked to replicate the same training the week of their second trail. Training and average rate of exertion reported by the subject are provided in Table 1.

Table 1. Descriptive Table of Subjects

	Training status	Age (yrs)	Height (inches)	Weight (kg)	Hours/miles per week	Average level of training (1-10)
Subject 1	UT	25	69.5	92.9	0 hrs	N/A
Subject 2	T	28	73	72.7	10.5 hrs	5
Subject 3	T	29	71	77	20.5 hrs	7
Subject 4	T	30	74	79.5	13 hrs	4
Subject 5	T	26	70	72.2	10.5 hrs	5
Subject 7	T	37	75	89.5	19 hrs	4
Subject 8	T	31	75	86.4	10 hrs	4
Subject 9	T	23	70	68.1	54 miles	8
Subject 11	UT	29	66	59.0	0	N/A
Subject 12	UT	35	75	93.1	1.5	3
Subject 13	UT	24	68	61.3	2.5	3
Subject 14	UT	24	67	97	1	2
Subject 15	UT	33	73	85	2.5	6

All subjects were asked to report a 24-hour diet recall including caffeine consumption and water intake. This data collected so the subject could replicate diet and hydration prior to the second trial. Each subject was asked not to consume caffeine within 8 hours prior to testing and not to exercise vigorously 24 hours prior to either trial.

Each subject was notified of the commitment, benefits, risks, and possible discomfort of the study. A signed consent form, approved by the university's committee for the protection of human subject was collected prior to the beginning of the first trial.

Design

Each subject was asked to report to the I.E. Faria Human Performance Research Lab at California State University, Sacramento. Upon the first visit to the lab, subjects were oriented to equipment and procedures before receiving the first treatment. Upon the second visit, the subject received the opposite treatment.

As a double-blind crossover study, the tester and subject were blinded to treatment order. Treatment order was decided by a third party via random number generation (Microsoft Excel). In order to ensure the treatment was double blind, all data was recorded by a secondary tester.

Treatments

Each subject underwent a treatment in a relative normoxic (FIO_2 = 19% ~3,000 ft) and hypoxic (FIO_2 = 11.5%, ~14,500 ft) environment within a hypoxic chamber. In order to replicate the environment in each trial, the pumps were turned on blinded from subject and tester's view.

Procedures

Upon arrival and completion of paperwork, subject was oriented to equipment and procedures before initial blood pressure was taken and recorded. Subject was then asked to dress in the Hexoskin Vest (Carre Technologies, Inc. Montreal, Canada). The

vest recorded EKG and transmitted via Bluetooth to a personal laptop computer. After each session, the beat to beat HR data was downloaded to CSV file and to Excel.

Once fitted with the vest, subjects were then asked to enter the hypoxic chamber with tester and rest for one hour on an exam table. A secondary tester recorded SaO_2 and HR at five-minute intervals. Once the rest period was completed, blood pressure was taken via auscultation with a stethoscope and sphygmomanometer. The sphygmomanometer was put around the subjects' bicep and inflated to approximately 180 mmHg. The stethoscope was placed on the brachial artery and the cuff was then deflated at a rate of approximately 3-5 mmHg per second. The first and fourth Korotkoff sounds were taken as systolic and diastolic blood pressure and recorded. The investigator taking blood pressure was adequately trained to take blood pressures and has over 1000 hours of clinical experience.

Each subject then completed a 10-minute bout of submaximal exercise on a Monarch cycle ergometer. Subjects rode at 1.5 Watts/Kg of body weight. Every subject rode with 2 Kg of resistance, but rotations per minute (RPM) were altered according to the required watt output (Watt= 2 Kg * RPM). Subjects were instructed to maintain this RPM throughout the 10 minute session. After 9 minutes, blood pressure, HR, and SaO_2 were recorded. Once the exercise session was complete, subjects were asked to cool down for five minutes, exit the chamber, and remove the Hexoskin vest before being thanked for their time and leaving. Subjects returned within the next few weeks for the second trial.

HRV Calculation

HRV was evaluated in the time domain, in which the time is the independent variable. In order to analyze the beat-to-beat variability of each trial, the standard deviation of normal-to-normal beats (SDNN) was found. SDNN has been deemed an overall estimate of HRV by the European Society of Cardiology and the North American Society for Pacing and Electrophysiology ("Heart Rate Varoiability: Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology," 1996). A measurement of variation, SDNN is calculated by finding the standard deviation of N-N (R-R) interval. Typically analyzed in a continuous EKG with data from a 24 hour Holter monitor or in 5-minute segments, all data in this study was analyzed in 2.5 minute segments (last 2.5 minutes of rest, and last 2.5 minutes of exercise) as there were not clear enough EKG readings to find an accurate SDNN in the 5-minute time frame. Within the 2.5-minute spans, standard deviation of the normal-to-normal beat was found and analyzed as HRV.

Data Analysis

All data was analyzed using the Wilcoxon test for Correlated groups to assess mean differences in independent (i.e. rest vs. exercise and hypoxic vs normoxic conditions) and dependent variables (i.e HR, SBP, SaO_2, and HRV) within each group, while a Mann-Whitney U test for differences between two independent samples was used to search for significance between groups. All data is expressed in means$\pm$SD. An Alpha level of 0.05 was used to identify any statistical differences.

Chapter 4

RESULTS

After being subjected to an hour rest period and a 10-minute bout of exercise in both hypoxic and normoxic conditions, heart rate (HR), systolic blood pressure (SBP), and saturation of oxygen (SaO_2) were recorded. HR and beat-to-beat variability were analyzed in 2.5-minute segments. Heart Rate Variability (HRV) was analyzed in the time domain using standard deviation of normal-to-normal beats (SDNN). A summary of mean HR, SBP, SaO_2, and HRV are listed in Table 2 and 3 for trained and untrained subjects respectively.

Table 2. Reported Values for Trained Subjects.

	HR (bpm)	**SBP (mmHg)**	**SaO_2 (%)**	**HRV (SDNN)**
Normoxic Rest	61.8±14.7	114.3±10	94.0±4.8	48.4±9.8
Normoxic Exercise	101.0±21.1*	141.1±11*	90.3±10.7*	17.6±16.6*
Hypoxic Rest	59.3±9.6	115.3±11.8	88.3±2.1	32.8±22.8
Hypoxic Exercise	112.8±20.9$^{\#}$	150.3±15.9$^{\#}$	72.0±11.6$^{\#}$	8.1±6.2$^{\#}$

All values are reported as Mean±SD.
(*) Significantly different ($p<0.05$) from Normoxic rest value.
($^{\#}$) Significantly different ($p<0.05$) from Hypoxic rest value.

Table 3. Reported Values for Untrained Subjects.

	HR (bpm)	SPB (mmHg)	SaO_2 (%)	HRV (SDNN)
Normoxic Rest	70.8±8.9	124.6±9.1	97.0±2.8	42.8±21.1
Normoxic Exercise	139.1±26.1*	155.3±9.4*	94.6±8.2	9.0±4.2*
Hypoxic Rest	72.3±10.7	121.3±12.7	88.0±2.6	42.8±17.3
Hypoxic Exercise	151.5±28.4#	159±14.7#	81.3±4.6#	5.8±6.8#

All values are reported as Mean±SD
(*) Significantly different ($p<0.05$) from Normoxic rest value.
(#) Significantly different ($p<0.05$) from Hypoxic rest value.

Heart Rate Mean (HR)

From rest to exercise, there was a significant increase ($p<0.05$) in HR during both environmental condition (i.e. normoxia and hypoxia) for the trained and untrained subjects (see Table 2 and 3). However, there was no significant difference in trained subjects resting HR between hypoxia and normoxia (see Table 2). Similarly untrained subjects did not have a significant difference in heart rate at rest in either hypoxic or normoxic conditions (Table 3). During exercise in differing environmental conditions, trained subjects showed no statistical significance between hypoxia and normoxia, while untrained subjects had a significantly higher mean HR during exercise in hypoxic conditions (as shown in Figure 1.)

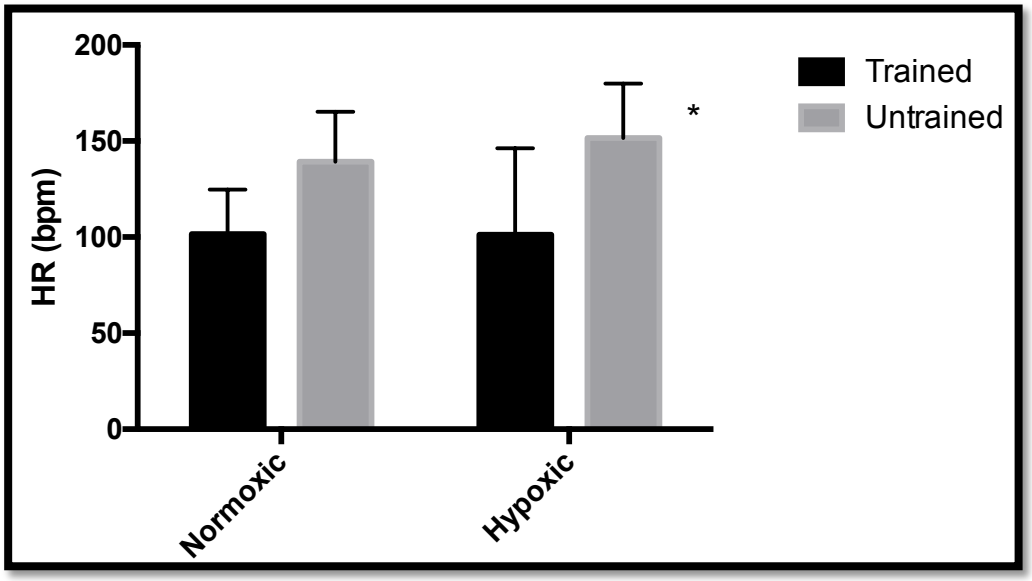

Figure 1. Mean Heart Rate of Trained and Untrained Subjects in Different Environments During Exercise
(*) Significantly different ($p<0.05$) from Normoxic Exercise

Systolic Blood Pressure (SBP)

From rest to exercise, there was a significant increase ($p<0.05$) in systolic blood pressure in both trained subjects and untrained subjects within the same environmental condition (see Table 2 and 3). When examining the effect of environment however, no statistical significance was found when comparing resting values of either trained or untrained subjects (see Table 2 and 3). Systolic blood pressure was significantly higher in trained subjects during hypoxic exercise, whereas untrained subjects did not have a significant increase in systolic blood pressure during hypoxic exercise (see Figure 2).

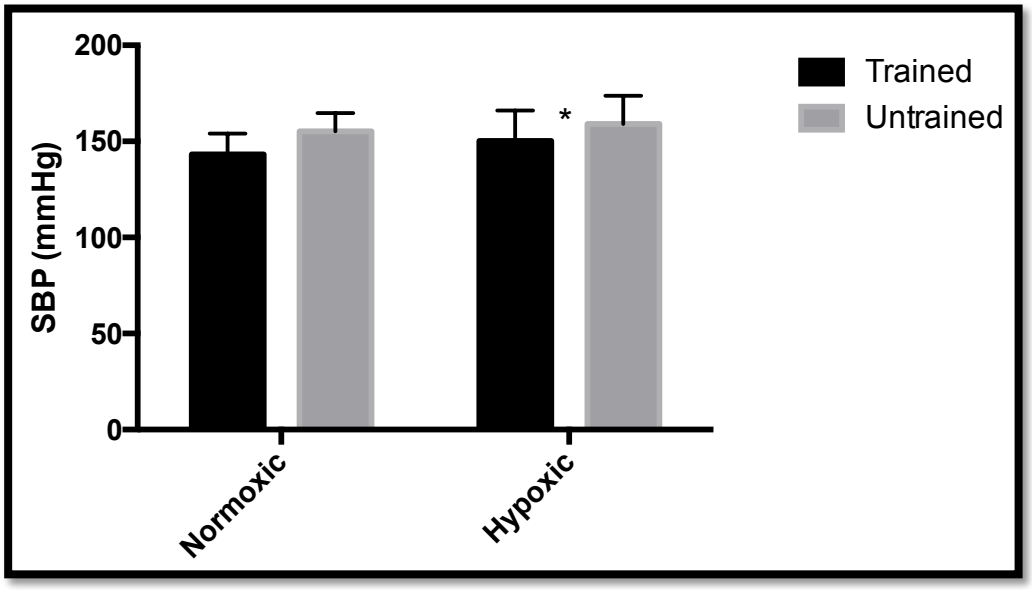

Figure 2. Systolic Blood Pressures of Trained and Untrained Subjects in Different Environments During Exercise.
(*) Significantly different ($p<0.05$) from Normoxic Exercise

Oxygen Saturation (SaO_2)

In trained subjects, resting SaO_2 was significantly lower during hypoxia compare to normoxia (see Table 2). In untrained subjects, SaO_2 under normoxic conditions did not change significantly from rest to exercise (see Table 3). In hypoxic conditions, untrained subjects had a significant decrease in SaO_2 from rest to exercise (see Table 3). Trained subjects showed a trend towards a decrease in SaO_2 during rest in hypoxia (see Figure 3), while there was a significant decrease during hypoxic exercise (see Figure 4). Untrained subjects showed a significant decrease at both rest and exercise in differing environmental conditions (see Figure 3 and 4).

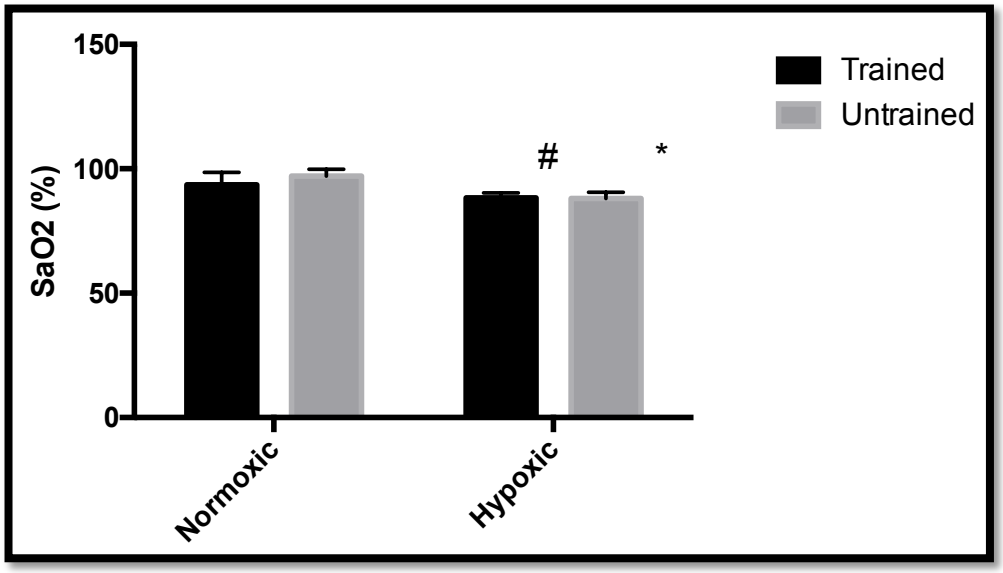

Figure 3. Resting SaO_2 in Trained and Untrained Subjects Exposed to Differing Environmental Conditions.
(*) Significantly different ($p<0.05$) from normoxic rest
(#) Trending towards a difference (Significant at the $p<0.10$ level) from normoxic rest

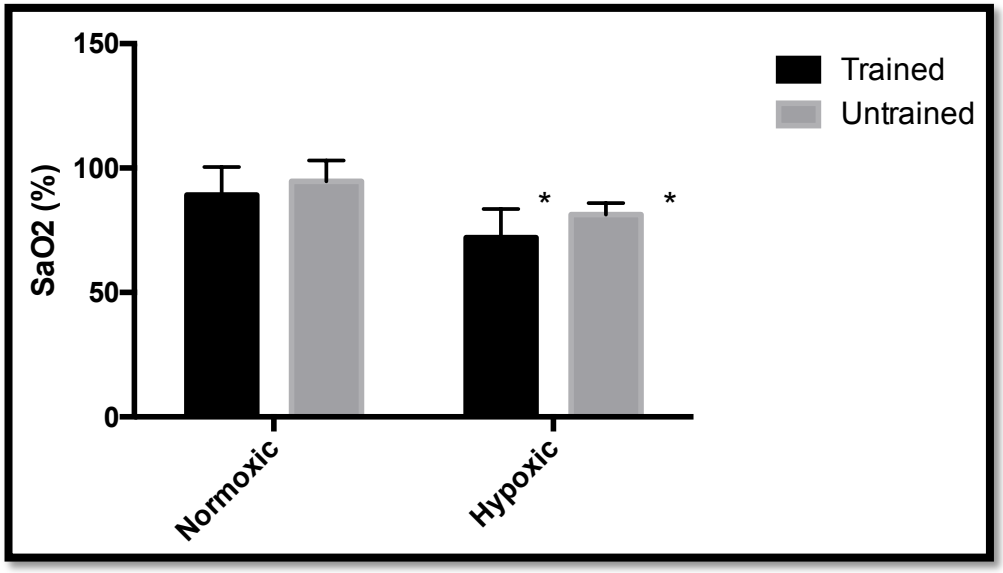

Figure 4. SaO_2 During Exercise in Trained and Untrained Subjects Exposed to Differing Environmental Conditions.
(*) Significantly different ($p<0.05$) from normoxic rest.

Heart Rate Variability (HRV)

From rest to exercise, there was a statistically significant decrease in SDNN in both environmental conditions with trained and untrained subjects (see Table 1 and 2). While untrained subjects had no significant change SDNN during rest or exercise with normoxic or hypoxic exposure, trained subjects had a trend towards a decrease in SDNN when exercise bouts were compared in different environmental conditions (see Figure 5).

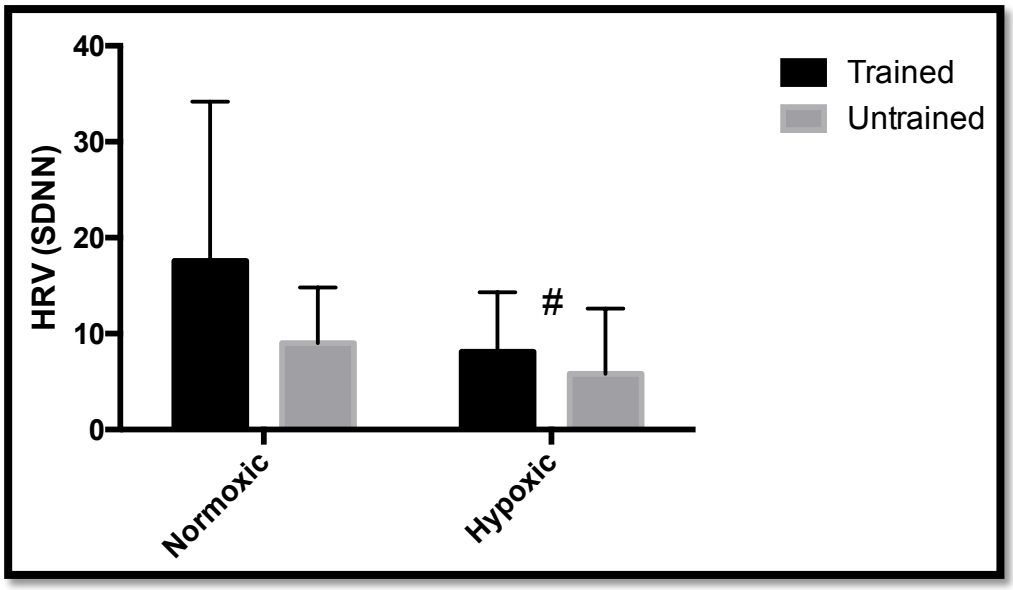

Figure 5. HRV in Trained and Untrained Subjects in Different Environmental Conditions During Exercise
(#) Trending towards a difference (Significant at the $p<0.10$ level) from normoxic exercise

A Mann-Whitney U test was used to compare SDNN between subject groups. There was no significant difference in SDNN when compared between trained and untrained subjects during normoxic rest (T: 48.4$\pm$9.8, UT: 42.8$\pm$21.1). No significant difference in HRV was found between subject groups during hypoxic exercise (T: 8.1$\pm$6.2, UT: 5.8$\pm$6.8).

Chapter 5

DISCUSSION

The results of this study supported previous research of the adaptations to training and exercise. Though this study was a cross-sectional design using subjects of low and high fitness. Both groups are exposed to normoxic and hypoxic conditions during rest and exercise.

Rest

With this subject pool and based on prior literature, we expected to see a significantly higher HR in hypoxic conditions when compared to normoxic. Most of the prior research shows that HR increases due to the withdrawal of parasympathetic tone (Bernardi et al., 2001; Bernardi et al., 1998). However, some research indicates that HR is actually significantly lower in trained subjects in hypoxic conditions without influencing cardiac output (Boushel et al., 2001). We found that neither trained nor untrained subjects had a significant increase in HR during rest in hypoxic conditions. While this disagrees with most of the prior research (Hopkins et al., 2003), our results could be due to outside stress influencing subjects on different treatment days. Investigators attempted to alleviate subject stress by creating a quiet comfortable environment by providing a blanket and a pillow. If subjects admitted any stress, investigators tried to either relieve mental stress, or distract subjects from the stress.

Systolic blood pressure had a similar finding in that neither trained nor untrained subjects had a significant increase in SBP at rest in differing environments. While there is not much direct research focused on blood pressure and differing environments, its has

been demonstrated that as a stressor, blood pressure will increase. Based on Boushel et al. (2001) findings, HR was not increased in hypoxic conditions while not influencing cardiac output. We can assume this is due to stroke volume (SV) increasing to maintain cardiac output. Blood pressure can be thought of as an indirect measure of stroke volume. Systolic blood pressure is commonly defined as the pressure in the arteries when the left ventricle contracts, while stroke volume is defined as the volume of blood pumped out of the heart. This suggests that the changes in SBP are due to parallel changes in SV.

SaO_2 during rest in differing environments was expected to have no significant decrease in either group. Prior research studies show little decrease in SaO_2 with exposure to a hypoxic environment during rest (Duplain et al., 1999). Unlike prior research, trained subjects had a trend towards a decrease in SaO_2 at rest in a hypoxic environment, while untrained subjects maintained their oxygen saturation. This could be due to decreased ventilation rate of the trained subjects, suggesting that do not respond well to hypoxia at rest. This finding could be explained by chemoreceptor desensitivity commonly found in highly trained endurance athletes (Aubert et al., 2003). McMachon et al. (2002) demonstrated this phenomenon using 20 well-trained cyclists. They were able to demonstrate that ventilation was increased mostly through respiratory muscle strength and also determined there was a blunted chemoreceptor sensitivity

At rest, the majority of research shows a decrease in parasympathetic tone with acute hypoxic exposure (Bernardi et al., 2001; Hopkins et al., 2003; Schmitt et al., 2008) and therefore a decrease in HRV. However, during rest there was no significant change in SDNN in different environments, suggesting that hypoxia does not have a significant

affect on autonomic function at rest. Our results could be different than prior research due to nature of the subjects in this study. While both groups were defined quite differently, our trained subjects training hours ranged from 10- 40.5 hours per week. This discrepancy in training could create variability in the cardiovascular and autonomic adaptations and variability in the SDNN.

Exercise

With the physiological stress of both exercise and a hypoxic environment, we expected to see a significant increase in HR. We found that untrained subjects had a statistically significant increase in HR during exercise in a hypoxic environment, while trained subjects did not. In contrast, we found that trained subjects had a significant increase in SBP, while untrained subjects did not have a significant increase during exercise in hypoxia. We believe this is due to training adaptations to the cardiovascular system. It has been well documented that with aerobic training, HR decreases (Da Silva et al., 2014; K. P. George et al., 1991; Morganroth & Maron, 1977), the heart enlarges and stroke volume increases (K. P. George et al., 1991; Gott et al., 1968; Rich & Havens, 2004). By finding a statistically significant increase in SBP, an indirect measure of stroke volume, in the trained subjects and a non-significant increase in SBP with the untrained subjects, our findings suggest that trained subjects respond to an increase in stroke volume rather than relying on an increase in HR. Untrained subjects on the other hand rely entirely on an increase in HR.

Trained subjects had a trend towards an decrease in SDNN with exercise in hypoxia. There was no significant difference in SDNN in the untrained subjects. The

trend toward a decrease in SDNN in the trained subjects suggests that the increase in SBP in trained subjects is mediated by decreasing parasympathetic input and increasing sympathetic input. The untrained subjects on the other hand show no difference in SDNN and SBP, but a significant increase in HR. This data suggests that that stroke volume rather than HR are more tightly controlled by the autonomic nervous system during hypoxic exercise. This data further demonstrates more responsive autonomic nervous system in trained athletes and are consistent with previous research examining autonomic function in trained athletes (K. P. George et al., 1991; Gott et al., 1968; Passino et al., 1996).

Conclusion

Though not all finding were as we expected, the majority of our findings supported prior research on the adaptations of aerobic endurance training. Despite our relatively small sample size, we were still able to demonstrate many cardiovascular adaptations such as decrease in heart rate, increase in stroke volume, and a suspected increase in parasympathetic tone. While there is still a gap in the literature on an upper limit and negative influences of high-volume exercise, it does appear that endurance trained subjects expand cardiac output during hypoxic exercise by increasing stroke volume, while untrained subjects rely on HR to increase cardiac output during hypoxic exercise. These differences in cardiac output expansion appear to be linked to the difference in autonomic function in trained and untrained subjects.

APPENDIX A

Informed Consent

Heart Rate Variability Compared in a Trained and Untrained Population under Hypoxic and Normoxic Conditions

You are invited to participate in a research study which will be looking at how the heart and nervous system react when exposed to a few different varaibles (simulated alitude, sea level air, moderate level exercise and rest). This study will be conducted by Shannon Wilson (a Graduate student at California State University, Sacramento) along with assistance from Daryl Parker, PhD. as well as other graduate students in the department of Kinesiology.

The purpose of this research is to observe the heart's response to different stimulus in two different population (trained and untrained people). If you decide to participate, you will be asked to rest in a hypoxic chamber that simulates alititude for one hour, participate with a short, controlled breathing exercise, as well as exercise at a low level within the chamber. Your participation in this study will last approximately 4 hours, split over two schedualed visits.

There are some possible risks involved for participants. These include a possible increase in blood pressure, increase in heart rate, and slight discomfort that may occur during the protocol. You can however stop at any time you would like. There are some benefits to this research, particularly that the contribution of this experiment may possibly lead to speculations of the safety of endurance training as well as give you information on your own ability to exercise at altitude.

If you have any questions about the research at any time, please call me at (916) 704-1107, or Dr. Parker at parkerd@csus.edu.. If you have any questions about your rights as a participant in a research project please call the Office of Research Affairs, California State University, Sacramento, (916) 278-5674, or email irb@csus.edu. In the event of a research-related injury, please contact your regular medical provider and bill through your normal insurance carrier, and then advise us.

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission. Measures to insure your confidentiality are assigned identification number known only to the investigators. No association to identification number and identiity will be released or linked back to any participants in the study. The data obtained will be maintained in a safe, locked location and will be destroyed after a period of three years after the study is completed.

Your participation is entirely voluntary and your decision whether or not to participate will involve no penalty or loss of benefits to which you are otherwise entitled. If you decide to participate, you are free to discontinue participation at any time with out penalty or loss of benefits to which you are otherwise entitled.

Your signature below indicates that you have read and understand the information provided above, that you willingly agree to participate, that you may withdraw your consent at any time and discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled, that you will receive a copy of this form, and that you are not waiving any legal claims, rights or remedies.

You will be offered a copy of this signed form to keep.

Signature _____ Date _____

APPENDIX B

Health History Form

The following form provides the investigator with the knowledge to assess your health status and if you an appropriate candidate for this study. Please clearly mark any of the applicable boxes. If you are asked for further explanation and do not want to, you do have the right to not share that information, just please state "I do not wish to share this information." The investigators main goal is for the subject's safety during this experiment and may ask additional questions in order to ensure your safety.

The information in this document will be kept private and stored in a safe, locked location. Your name will not be associated with this document, but you will be assigned a randomized number as an identification marker which will only be known to the primary investigator as well as the advisor.

Thank you very much for your time.

Please mark all true statements.

History

You have had:

_____ A heart attack

_____ A heart surgery

_____ A heart or cardiac catheterization

_____ Coronary angioplasty (PCTA)

_____ A pacemaker/ implantable cardiac defibrillator

_____ A diagnosed rhythm disturbance or arrhythmia

_____ Heart Valve Disease

_____ Heart transplant

_____ Congenital heart disease

Symptoms

_____ You experience chest discomfort with exertion or exercise

_____ You experience unreasonable breathlessness

_____ You experience dizziness, fainting, or blackouts

_____ You are currently prescribed and taking medication for your heart

Other Health Issues

_____ You have diabetes

If marked yes:

Type I or Type II?: _____

How long have you been diabetic?:
_____

_____ You have asthma or other lung disease

If marked yes:

Are you currently seeing a physician for it? _____

Has a physician cleared you for physical activity and exercise?

_____ You have burning or cramping sensation in your legs when walking short distances.

_____ You have musculoskeletal problems that limit your physical activity

If marked yes:

What is the issue?:
_____

_____ You have any issue or concerns about the safety of exercise.

If marked yes:

What are your main concerns?

_____

Is there any questions the investigator can answer that would settle your qualms?

_____ You are currently taking prescription medications.

If marked yes:

What are the medications for (can write do not wish to share): _____

_____

_____

_____ You are pregnant.

Other risk factors

_____ You are a man older than 45 years of age.

_____ You are a woman older than 55 years of age or have had a hysterectomy and/or are post menopausal.

_____ Currently smoking, or have quit smoking within the last 6 months

_____ Known blood pressure of above 140/90 mmHg at rest.

_____ Currently take blood pressure medication

_____ Do not know your blood pressure.

_____ Your blood cholesterol level is >200 mg/dL

_____ You do not know your cholesterol level

_____ You have a close blood relative who has had a heart attack, or heart surgery before the age of 55 (brother or father) or the age of 65 (mother or sister).

_____ On average, you get **less** than 30 minutes of exercise on at least 3 days per week.

_____ You are at least >20 pounds over weight

_____ **I do not apply to any of the above questions.**

Questionnaire adapted from AHA/ACSM Health and Fitness facility Pre-Participation Screening Questionnaire, previously modified from the American College of Sports Medicine Position Stand and the American Heart Association. Recommendations for cardiovascular screening, staffing, and emergency policies at health/fitness facilities. Med Sci Sports Exerc. 1998;30(6):1009-18

APPENDIX C

Training and Diet Recall

Training Recall

Please list your exercise regimen for the past 7 days

Day	Description of exercise	Volume (Hours training)	Intensity*
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Please see attached Intensity scale sheet on the next page.

Would you consider yourself a competitive athlete? ____yes ____no

If yes, have you competed in races/events over in the last two years?
___yes ___no.

If yes, how many in the last two years?

_____

How would you state your level of competiveness?

_____

Based on the following intensity sheet, what would you consider your average level of training?

_____

24 Hour Diet Recall

In the following space, please try your best to write down everything you ate and drank 24 hours prior to testing.

Meal	
Breakfast	
Snack	
Lunch	
Snack	
Dinner	

Estimation of Water drank: _____glasses

Caffeinated beverages: ____yes ____no : If yes, please state what type (i.e coffee, tea, soda, energy drink/shot) and how many servings (Cups, shots, cans)

_____

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