Journal of Human Performance in Extreme Environments

Volume 15 | Issue 1 Article 7

Published online: 12-12-2019

Higher Muscle Tissue Oxygenation When Exposed to Hypobaric Hypoxia Than Normobaric Hypoxia

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Abstract

There has been recent debate on the potential difference in physiological response between exposure to simulated altitude (normobaric hypoxia) and terrestrial altitude (hypobaric hypoxia). Purpose: To determine the difference in the physiological response to normobaric and hypobaric hypoxia during exercise. Methods: Eight recreationally active subjects (27 $\pm$ 5 years old, 73.1 $\pm$ 7.4 kg body weight, 170.6 $\pm$ 6.7 cm height, and 19.3 $\pm$ 9.2% body fat) completed incremental cycling exercise to volitional fatigue in three separate environments: normobaric normoxia (NN; 350 m), normobaric hypoxia (NH; simulated 3094 m), and hypobaric hypoxia (HH; 3094 m). Heart rate, blood oxygen saturation, and muscle tissue oxygenation were measured at rest and continuously throughout the exercise trials. Results: Blood oxygen saturation (SpO2) was ~10% higher in NN compared to the two hypoxic conditions ($p < 0.001$) at rest and all exercise stages, with no difference between NH and HH ($p > 0.05$). Heart rate was higher at rest in HH (98 $\pm$ 13 bpm) compared to NN (83 $\pm$ 15 bpm, $p = 0.011$) and NH (84 $\pm$ 14 bpm, $p = 0.001$) which persisted until 165 watts at which point no difference was observed ($p > 0.05$). Muscle tissue oxygenation was 17% higher in HH compared to NN and 19% higher than NH throughout exposure ($p < 0.05$). Conclusion: These data indicate that the hypoxic stresses resulting from normobaric and hypobaric hypoxia are not the same and that hypobaric hypoxia may not result in hypoxia at the level of the tissue.

Keywords: altitude, exercise, cycling, elevation, performance

Introduction

When ascending to altitude, physiological changes occur throughout the human body. Specifically, exposure to altitude has shown increased heart rate, lowered peripheral oxygenation (SpO_2), and reduced maximal oxygen consumption (VO_{2max}) (DeLorey, Shaw, Shoemaker, Kowalchuk, & Paterson, 2004; Grover, Weil, & Reeves, 1986; Zupet, Princi, & Finderle, 2009). Much of the well-controlled research investigating the physiological effects of altitude has been conducted in chambers that simulate altitude. This is most commonly accomplished by reducing the fraction of oxygen in the chamber and is known as normobaric hypoxia (NH). During actual altitude exposure, or hypobaric hypoxia (HH), the fraction of oxygen is unchanged, but the barometric pressure is reduced. This reduction in barometric pressure makes it more difficult for oxygen to bind to hemoglobin and be transported to target tissues. In theory, both environments lead to the same partial pressure of oxygen and, therefore, should elicit the same responses, but recent research has questioned this assumption.

Acute exposure to HH at rest results in lower blood oxygen saturation (SpO_2) and higher heart rate compared to NH (Savourey, Launay, Besnard, Guinet, & Travers, 2003; Self, Mandella, Prinzo, Forster, & Shaffstall, 2011). However, these results have not always been consistent (Richard et al., 2014; Roach, Loeppky, & Icenogle, 1996; Savourey et al., 2007). Others have also documented a further decrease in physical performance (Beidleman, Fulco, Staab, Andrew, & Muza, 2014), lower ventilatory response (Faiss et al., 2013), and higher oxidative stress (Ribon et al., 2016) in HH versus NH. The observed effects of the method used to achieve hypoxia have not been consistent in the exercise model and, therefore, more research is needed to determine if differences only exist at rest or if they are also present for different exercise intensities.

The majority of research regarding differences in hypoxic environments has examined cardiovascular and respiratory responses, but little research has examined the skeletal muscle response. Unpublished observations from our laboratory have found limited differences in muscle transcriptional response between NH and HH despite differences in SpO_2 and heart rate. It is currently unknown if the barometric pressure-induced alterations in heart rate and SpO_2 extend to the skeletal muscle. The apparent increase in heart rate to account for the decrease in SpO_2 may lead to adequate oxygen delivery to the muscle and therefore not create a hypoxic environment at the level of the muscle. Using near-infrared spectroscopy (NIRS) technology, researchers have determined that muscle oxygenation does decrease with incremental exercise (Austin et al., 2005; Ferreira, Koga, & Barstow, 2007; Murias, Spencer, Keir, & Paterson, 2013). However, there is a lack of information on muscle oxygenation during hypoxia exposure, and on the effects of the type of hypoxia exposure.

http://dx.doi.org/10.7771/2327-2937.1117

Based on existing data regarding peripheral oxygenation and cardioventilatory responses, HH may be a more severe environmental condition and lead to different physiological responses than NH. The mechanisms behind these changes are still unclear. Therefore, the purpose of this study is to determine if the method to achieve hypoxia results in differences in muscle oxygen saturation during rest and incremental exercise. The addition of this data will have an impact on the physiological understanding of the effects of different forms of hypoxia, and may have implications for the interpretation of previous research based on the experimental model and methodology used.

Methods

Participants

Eight recreationally active (four males and four females) subjects were recruited for this study. Recreationally active is defined as participating in moderate to vigorous physical activity for 30 minutes at least three days per week. Participants completed a risk stratification form to ensure safe completion of the study and an Institutional Review Board approved informed consent prior to participating in this study.

Study Design

Subjects completed incremental exercise trials to volitional fatigue in three environmental conditions, normobaric normoxia (NN; 350 m), normobaric hypoxia (NH; 3094 m simulated), and hypobaric hypoxia (HH; 3094 m). Trials were separated by no less than two days. Heart rate, blood oxygen saturation, and muscle tissue oxygenation of the vastus lateralis were analyzed throughout the trials.

Initial Visit

Participants reported for an initial visit to collect height, weight, and body fat percentage for descriptive purposes. Body fat percentage was measured using an electronic load cell-based hydrostatic weighing system (Exertech, Dresbach, MN). Each subject performed six to ten trials, with the highest three underwater weights averaged and recorded. Body density from the underwater weights was converted to percent body fat using the Siri equation (Siri, 1961). Residual lung and gastrointestinal volume was estimated and corrected for using an established prediction equation (Thomas & Etheridge, 1980).

Experimental Trials

Experimental trials were conducted in a randomized and counterbalanced order and separated by at least two days. Each subject completed an incremental cycle exercise test to volitional fatigue in three environmental conditions: NN (350 m, 20.9% O_2, 730 mmHg, P_{O2} = 152.8 mmHg), NH (350 m, 14.8% O_2, 730 mmHg simulating 3094 m, P_{O2} = 108.0 mmHg), and HH (3094 m, 20.9% O_2, 520 mmHg, P_{O2} = 108.8 mmHg). The partial pressure of oxygen (P_{O2}) in the air is calculated by multiplying the percentage of oxygen by the barometric pressure. The NN and NH trials were conducted in an environmental chamber (Darwin, St. Louis, MO) that controlled for environmental oxygen concentration in order to simulate altitude (Altitude Control Technologies, Lafayette, CO). The environmental chamber simulates altitude by decreasing the oxygen fraction in the air, while maintaining normal barometric pressure. Additionally, subjects traveled to Leadville, Colorado (3094 m in elevation) to complete the same exercise protocol in the HH condition.

The incremental cycle protocol test was performed on an electronically braked cycle ergometer (Excalibur; Lode, The Netherlands). The protocol began at 95 W and increased by 35 W after every three-minute stage. The participants cycled until volitional fatigue. Maximum workload was calculated using the following expression: watts of highest completed stage + (35 × (seconds of final stage / 180)).

Heart Rate, and Blood and Muscle Tissue Oxygenation

Heart rate, blood oxygen saturation, and muscle oxygen saturation were monitored continuously throughout each trial. Heart rate was measured using a standard chest strap-based heart rate monitor (Polar V800; Polar, Lake Success, NY). Blood oxygen saturation was measured using a pulse oximeter worn on the subject's index finger (Wrist Ox_2; Nonin Medical, Inc., Plymouth, MN). Muscle tissue oxygenation was measured using NIRS (OxyMon MKIII, Artinis, The Netherlands). Subjects were instrumented with NIRS probes to monitor absorption of light across muscle tissue, as previously described (Billaut & Buchheit, 2013; Subudhi, Dimmen, & Roach, 2007). The NIRS emitter and detector pair were fixed on the distal part of the right vastus lateralis muscle belly (approximately 15 cm above the proximal border of the patella and 5 cm lateral to the midline of the thigh) using a black, plastic spacer with optode distance of 4.0 cm. The probe was secured via double-sided stick disks and bandages to shield from extraneous light. This noninvasive device allows for continuous monitoring of muscle tissue oxygenation throughout the exercise trials. Heart rate, blood oxygen saturation, and muscle tissue oxygenation data were averaged over five minutes of rest and over the last minute of each three-minute stage. Maximal heart rate was interpreted as the highest heart rate observed during each exercise trial.

Statistical Analysis

Maximal workload achieved during exercise was analyzed using a one-way ANOVA. Heart rate, blood oxygen saturation, and muscle tissue oxygenation data obtained

from rest, several absolute submaximal workloads, and a relative maximal exercise load were analyzed with a repeated measures two-way ANOVA (time by trial). The number of absolute workloads used for analysis was determined by the number of workloads/stages that all subjects were able to complete. After running the ANOVA, if significance was found, a Fisher's protected least signi ficant difference *post hoc* test was used to determine where significance occurred. Significance was set at 5% error rate ($p < 0.05$). The Statistical Package for Social Sciences software (SPSS 23.0, Chicago, IL) was used to analyze data.

Results

Eight individuals completed all protocols associated with this study. Descriptive statistics of the participants are displayed in Table 1. All participants were able to complete the graded exercise through 165 W. Therefore, measures associated with an absolute workload during the exercise protocol were analyzed at rest, 95 W, 130W, 165 W. An additional relative maximal exercise intensity (the stage in which each participant reached volitional fatigue) was used to compare measures at each individual's maximal exercise effort. The average maximal workload achieved during the graded exercise test was higher in NN (220 $\pm$ 40 W) compared to NH (205 $\pm$ 40 W, $p = 0.002$) and HH (204 $\pm$ 37 W, $p = 0.001$). There was no difference in maximum workload achieved between NH and HH ($p = 0.863$).

Heart Rate

Heart rate was higher in the HH condition compared to the NN and NH conditions at rest ($p = 0.011$ and $p = 0.001$, respectively), at 95 W ($p = 0.050$ and $p = 0.012$, respectively), and at 130 W ($p = 0.030$ and $p = 0.038$, respectively). At 165 W, heart rate was not different in the HH condition compared to the NN and NH conditions ($p = 0.524$ and $p = 0.379$, respectively). There were no differences in heart rate between NN and NH at rest, 95 W, 130 W, and 165 W ($p = 0.749$, $p = 0.668$, $p = 0.580$, and $p = 0.935$, respectively). Heart rate increased with increasing absolute exercise intensity ($p < 0.05$) in all trials. At maximum exercise, heart rate in the NN condition was higher than in NH ($p = 0.010$). The higher heart rate in NN did not reach statistical significance over HH ($p = 0.135$). Heart rate was not different at maximal exercise between NH and HH ($p = 0.750$). See Figure 1 and Table 2.

Table 1
Participant descriptive data ($n = 8$).

Age (years)	Height (cm)	Weight (kg)	Body fat (%)
27 $\pm$ 5	170.6 $\pm$ 6.7	73.1 $\pm$ 7.4	19.3 $\pm$ 9.2

Note. Data are mean $\pm$ standard deviation.

Blood Oxygen Saturation

Blood oxygen saturation was higher in the NN condition compared to the NH condition ($p < 0.001$) and the HH condition ($p < 0.001$) at rest and all exercise intensities. Blood oxygenation was not different between NH and HH at rest ($p = 0.940$), 95 W ($p = 0.761$), 130 W ($p = 0.536$), or at 165 W ($p = 0.106$). Blood oxygenation decreased from rest to 95 W, to 130 W, and to 165 W in the NH ($p = 0.005$, $p = 0.001$, and $p < 0.001$, respectively) and HH conditions ($p = 0.034$, $p = 0.004$, and $p = 0.001$, respectively). Blood oxygenation was similar from rest to 95 W and to 135 W ($p = 0.438$ and $p = 0.798$, respectively), but decreased from rest to 165 W in the NN condition ($p = 0.048$). At maximum exercise, blood oxygen saturation was higher in NN compared to NH and HH ($p < 0.001$), but was not different between NH and HH ($p = 0.117$). Blood oxygen saturation was lower at maximal exercise compared to resting in NN ($p = 0.032$), NH ($p < 0.001$), and HH ($p < 0.001$). See Figure 2 and Table 2.

Muscle Tissue Oxygenation

Muscle tissue oxygenation of the vastus lateralis was higher in the HH condition compared to the NN ($p = 0.001$) and NH ($p = 0.004$) conditions, with no difference between NN and NH ($p = 0.670$), regardless of exercise intensity. Muscle tissue oxygenation decreased with increasing workloads ($p < 0.050$) regardless of trial. See Figure 3 and Table 2.

Discussion

This study aimed to determine differences in muscle tissue oxygenation during incremental exercise in simulated altitude compared to terrestrial altitude. The main findings of this study were higher heart rate and muscle tissue oxygenation in HH compared to NH during rest and exercise. Thus, differences do exist between NH and HH and exposure to environmental hypoxia may not necessarily lead to hypoxia at the level of the skeletal muscle.

Cardiovascular differences have been identified between NH and HH, specifically at rest, but these findings are not always consistent. Some research has shown heart rate to be higher in HH than NH both at rest (Savourey et al., 2003) and during exercise (DiPasquale, Strangman, Harris, & Muza, 2015). In the current study, heart rate was higher in HH compared to the NN and NH conditions at rest and during the two lowest submaximal workloads. The change in barometric pressure may be a modulating factor for the difference observed in heart rate at rest. It is currently unknown what receptors are responsible for detecting changes in atmospheric barometric pressure. There are cardiopulmonary baroreceptors in the thorax that may detect subtle pressure changes associated with hypobaric

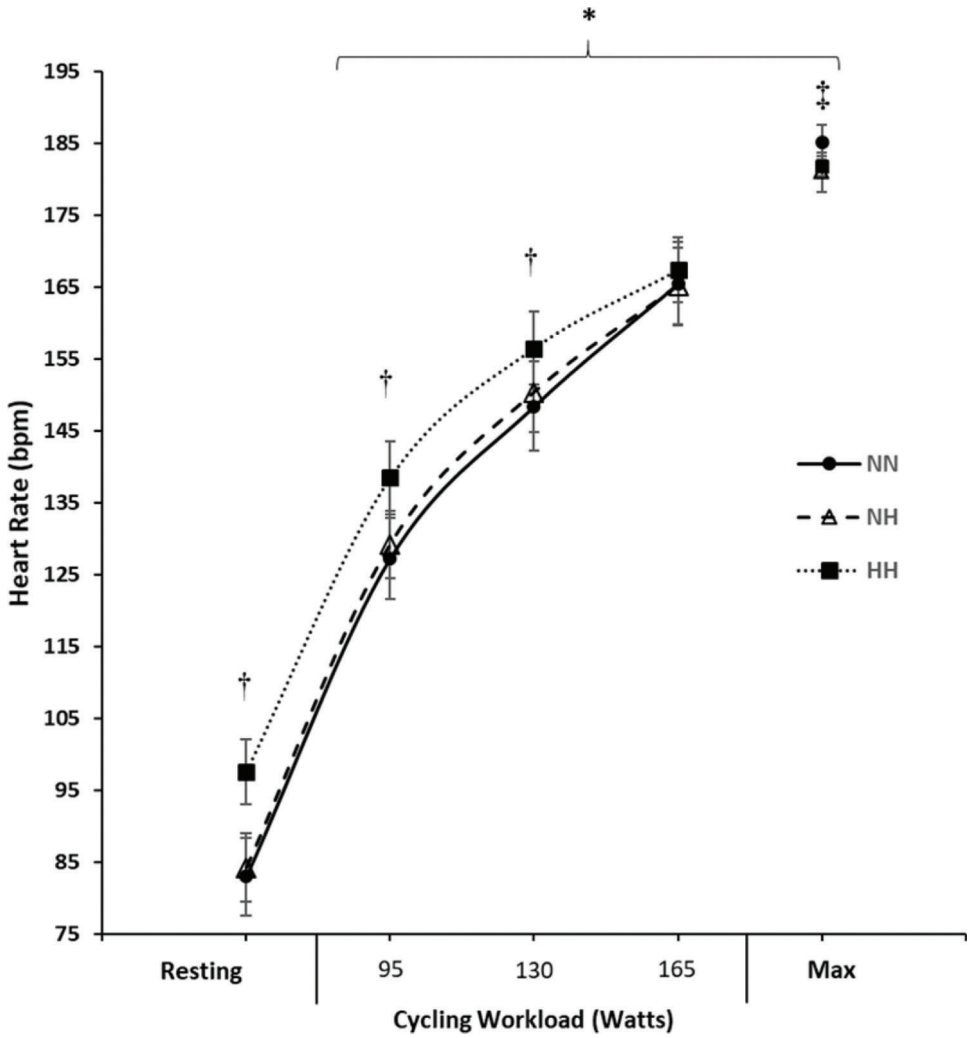

Figure 1. Heart rate during rest and exercise trials. *$p < 0.05$ from rest. †$p < 0.05$ HH from NN and NH. ‡$p < 0.05$ NN from NH.

exposure (DiPasquale et al., 2015). These baroreceptors mediate sympathetic activity and blood pressure during exercise (Fadel & Raven, 2012) and could be responsible for the higher heart rate observed during hypobaric exposure.

At maximal exercise, peak heart rate was higher in NN compared to both hypoxic conditions, although only significantly higher than NH. This decrease in peak heart rate with exposure to hypoxia has been previously observed during incremental cycle tests. At simulated altitudes over 3800 m, peak heart rate is lower in hypoxia than normoxia (Benoit, Busso, Castells, Geyssant, & Denis, 2003). The current study did not exceed 3100 m, but still resulted in lower peak heart rate. One explanation for this reduction in peak heart rate is hypoxic myocardial dysfunction. Hypoxia has a direct effect on electrophysiological properties including repolarization length and transmission time on the AV node (Benoit et al., 2003). Other researchers have linked lower maximum heart rate to decreases in arterial saturation (Woorons, Lamberto, Beaudry, & Richalet, 2007).

Table 2
Heart rate, blood oxygen saturation (SpO_2), and muscle tissue oxygenation (muscle O_2) during rest and cycling exercise.

	Resting	95 W	130 W	165 W	Maximal
Heart rate (bpm)					
NN	83 ± 5	127 ± 6*	148 ± 6*	165 ± 6*	185 ± 2*
NH	84 ± 5	129 ± 5*	150 ± 6*	165 ± 5*	181 ± 3*‡
HH	98 ± 4†	138 ± 5*†	156 ± 5*†	167 ± 4*	182 ± 1*
SpO_2 (%)					
NN	97 ± 1†	97 ± 1†	97 ± 1†	96 ± 1*†	95 ± 1*†
NH	91 ± 1	87 ± 1*	86 ± 1*	86 ± 1*	84 ± 1*
HH	91 ± 1	87 ± 2*	85 ± 2*	84 ± 2*	82 ± 1*
Muscle O_2 (%)					
NN	42 ± 3	39 ± 3*	37 ± 3*	36 ± 3*	33 ± 3*
NH	44 ± 2	38 ± 2*	36 ± 3*	34 ± 3*	31 ± 3*
HH	52 ± 2†	47 ± 2*†	44 ± 2*†	42 ± 2*†	39 ± 1*†

Note. Data are mean ± SE.
*$p < 0.05$ from resting, †$p < 0.05$ from all other conditions, ‡$p < 0.05$ from NN.

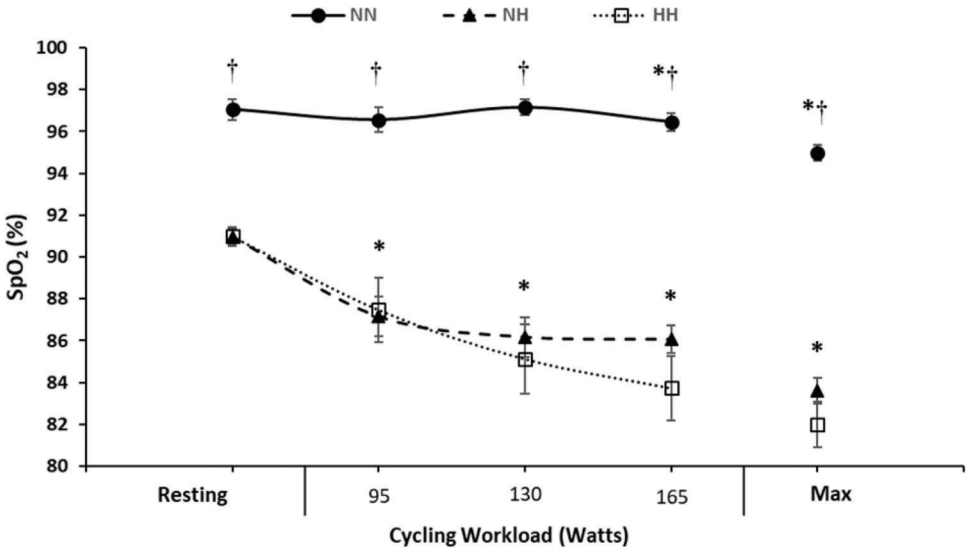

Figure 2. Blood oxygen saturation during rest and exercise trials. *$p < 0.05$ from rest. †$p < 0.05$ NN from NH and HH.

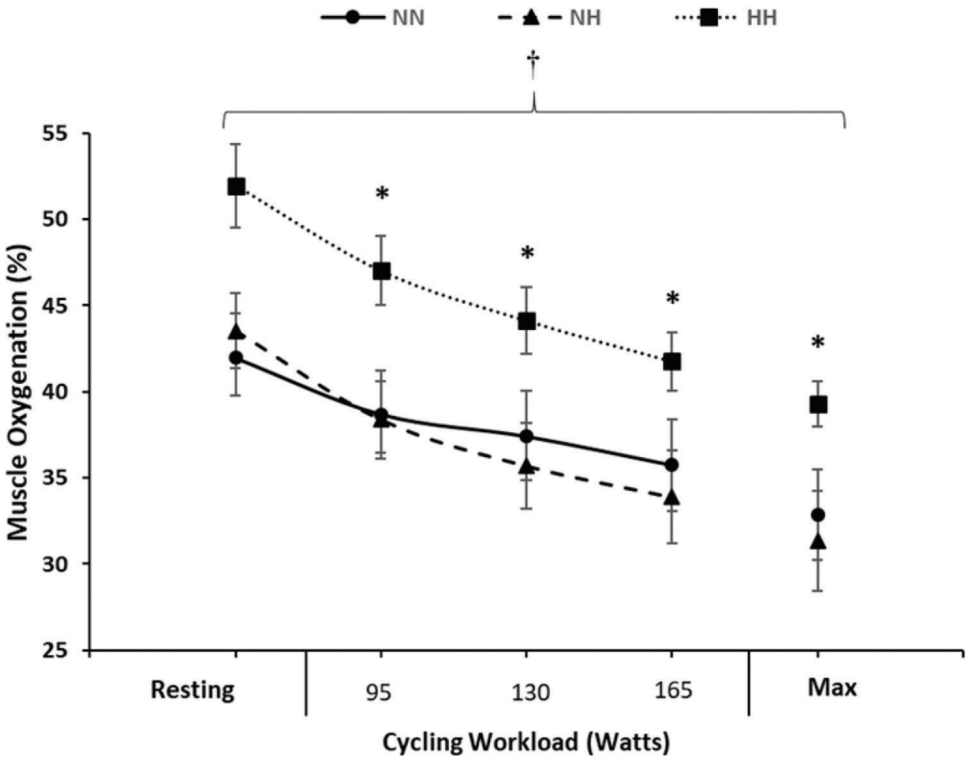

Figure 3. Muscle tissue oxygenation during rest and exercise. *$p < 0.05$ from rest. †$p < 0.05$ HH from NN and NH.

During acute moderate hypoxia, subjects demonstrating exercise-induced arterial hypoxemia (EIH) in normoxia had more pronounced reductions in peak heart rate than subjects without EIH (Grataloup, Busso, Castells, Denis, & Benoit, 2007).

It is well known that acute hypoxic exposure results in lower blood oxygen saturation levels. However, a consensus has yet to be reached if NH and HH elicit similar or different responses in SpO_2 at rest and during exercise. At rest, some research has found SpO_2 to be similar in acute exposures to NH and HH (Loeppky, Scotto, & Roach, 1996; Richard et al., 2014). Other research has demonstrated HH to result in lower SpO_2 than NH (Saugy et al., 2016; Savourey et al., 2003; Savourey et al., 2007). Lower SpO_2 in HH may be related to an increase in dead-space ventilation associated with an increase in breathing

frequency (Savourey et al., 2007). At altitudes greater than 5000 m, HH has resulted in lower SpO_2 than NH (Self et al., 2011). In the current study, SpO_2 was similar between NH and HH possibly because the altitude exposure did not exceed 3100 m. The hypoxic stimulus may not have been great enough to elicit a differential response between hypoxic conditions. During submaximal cycle exercise, SpO_2 has been shown to be similar between NH and HH (Beidleman et al., 2014; Faiss et al., 2013). Again, the low hypoxic dose may be attributed to the lack of difference observed in SpO_2 between NH and HH during exercise.

Previous research has focused primarily on examining cardioventilatory differences between NH and HH, but limited research exists regarding muscle oxygenation between the two conditions. During submaximal exercise, percentage of oxygenated hemoglobin within the muscle has been shown to range from 40 to 50% (Billaut et al., 2013) and continue to decrease during incremental exercise (Austin et al., 2005). Previous research has shown similar muscle oxygenation levels between NN and NH during resistance exercise (DeLorey et al., 2004; Scott, Slattery, Sculley, Lockhart, & Dascombe, 2017). Similar oxygenation levels have also been observed between NN and HH during incremental cycle exercise (Subudhi, Lorenz, Fulco, & Roach, 2008). Others have shown muscle oxygenation to be lower in NH (Subudhi et al., 2007). In the current study, muscle oxygenation was higher in HH than in NN and NH. Regardless of the mechanism used to achieve hypoxia, to our knowledge this is the first study to observe higher muscle oxygenation in hypoxia during incremental exercise. Intermittent hypoxic exposure protocols have also resulted in higher muscle oxygenation near maximal exercise following a 10-day protocol (Hamlin, Marshall, Hellemans, & Ainslie, 2010; Marshall et al., 2008). However, these exercise tests were completed in normoxic environments following hypoxic exposure. The current study observed higher muscle oxygen saturation during the HH exposure. The elevated muscle tissue oxygenation could be due to increased blood flow to working muscle. Heart rate was also elevated in HH, presumably to compensate for lower SpO_2. Since the slopes of change between all conditions were similar, the low SpO_2 was compensated for by increased blood flow (DeLorey et al., 2004; Kawahara, Saito, Kashimura, & Muraoka, 2008).

Despite higher muscle oxygen saturation observed in HH, maximal workload achieved during exercise was greater in NN than in either hypoxic condition. Further, there was no difference in maximal workload between NH and HH. This suggests factors other than decreased muscle oxygenation are responsible for fatigue in hypoxia. One explanation is that decreased maximal workload observed in hypoxia is more associated with a decrease in blood oxygen saturation. The ability to maintain aerobic exercise performance at altitude is linked to the ability to maintain adequate SpO_2 (Chapman, 2013; Saugy et al., 2016). The higher SpO_2 throughout exercise seems to be one of the main contributing factors to greater maximal workloads achieved in normoxia compared to hypoxic conditions. In the current study, oxygen delivery to skeletal muscle did not appear to be negatively affected in HH. Rather, there seems to be increased oxygen availability in HH at the active musculature, possibly from increased blood flow. The decreased SpO_2 may have a greater effect on other tissues and organs of the body than muscle. Specifically, oxygen delivery to cardiac muscle or to the brain could have been a major contributor to the decreased performance in hypoxia.

It is still unclear why muscle oxygen saturation and heart rate were only higher in the HH condition and not the NH condition. Increases in cardiac output have been observed with acute HH exposure (Gamboa et al., 2003). Increases in cardiac output could explain the increase in muscle oxygenation. Specifically, cardiac output increases could lead to increases in leg blood flow. This could result in increased muscle oxygen availability. In HH it seems the cardiovascular system is overcompensating but may only have a limited effect in NH. One important difference between our hypoxic trials was the time it took to ascend to HH, rather than the immediate exposure of NH. Logistical issues with travel from a low elevation to a high elevation did not allow an immediate evaluation of HH. Due to the time it took to ascend, participants were exposed to the HH condition for longer than the NH condition. This could be a factor leading to the increased heart rate observed in HH. Much of the previous research suffers from this study design issue as well, but tends to generally agree with our data. Previous research has shown heart rate to increase from 5 minutes to 5 hours in HH. Further, heart rate following 5 hours of exposure to HH tended to be higher than heart rate following 30 minutes of exposure to NH (Richard et al., 2014). Clearly, either the time course or the effects of altered barometric pressure are responsible. In defense of our study design and that of others, this does lend to a high degree of external validity as ascending to altitude is most often not an immediate endeavor.

Conclusion

In conclusion, the current study indicates that HH may be a more severe environment than NH, as demonstrated by the overcompensation of the cardiovascular system to deliver oxygen to the working skeletal muscle upon exposure. This investigation provides support to the mounting evidence indicating that simulated and terrestrial altitudes are not interchangeable environments. It enhances the current literature surrounding the existence of physiological differences between NH and HH. Further, this study showed adequate muscle tissue oxygenation throughout all trials and that factors other than decreased muscle oxygenation may be responsible for performance

decrements observed in hypoxia. Further research is needed to identify what specific mechanisms are accountable for decreased exercise performance in hypoxia.

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