THE EFFECTS OF HYPOXIC MANIPULATION ON SEA-LEVEL PERFORMANCE
AND VO$_2$max: A META-ANALYSIS

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THE EFFECTS OF HYPOXIC MANIPULATION ON SEA-LEVEL PERFORMANCE AND VO₂max: A META-ANALYSIS

A Thesis

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Abstract

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Statement of Problem

Since the 1968 Summer Olympic Games (Mexico City, altitude ~ 2200m above sea level (SL)), a numerous amount of research has been conducted on the effects of hypoxic manipulation (HM) (i.e. altitude training which includes LHTH, LHTL, LLTH, and IHE) for improving SL exercise performance. However, the SL performance results of HM studies are inconclusive. Further, the results of the physiological variables such as VO_{2\text{max}}, hematocrit (Hct), and hemoglobin concentration [Hb] are conflicting. Therefore, it is unclear the effects HM may have on SL exercise performance and certain physiological variables. A method of resolving the conflicting data on HM studies is the use of meta-analysis. Therefore, the purpose of this study was to conduct a meta-analysis on HM studies to identify the effects of HM versus normoxic training (NT) on SL exercise performance, VO_{2\text{max}}, Hct, and [Hb] in trained athletes.

Methods

A literature search from 1965 to 2008 was conducted to locate pertinent studies on HM. An inclusion criteria was developed to determine studies that were included in the analysis. Studies included in the analysis met the following inclusion criteria: 1) adequate
use of a control group (CG), 2) published performance, or VO$_{2\text{max}}$, or Hct, or [Hb] results with means ± SD and 3) use of trained athletes. If studies met the inclusion criteria, they were read and coded for the following variables: 1) HM model which included LHTH, LHTL, LLTH, and IHE, 2) performance were defined as time in a time trial, or peak power output during a GXT, or total work capacity 3) VO$_{2\text{max}}$ as well as Hct and [Hb]. To calculate effect size (ES) the following formula was used: Cohen’s d = (Post$_{m}$ – Pre$_{m}$)/Pre$_{SD}$. ES were than corrected (ES$_{\text{Corr}}$) for sample biasness and then weighted mean of the ES (ES$_{\text{WM}}$) was calculated. Twenty-nine studies met the inclusion criteria for performance with a total of 42 and 49 ES$_{\text{Corr}}$ extracted from NT and HM, respectively. Twenty-seven studies met the inclusion criteria for VO$_{2\text{max}}$ with a total of 39 ES$_{\text{Corr}}$ extracted from NT and HM. Eighteen studies met the inclusion criteria for [Hb] with 23 ES$_{\text{Corr}}$ extracted from NT and HM. For Hct, 14 studies met the inclusion criteria with 15 and 17 ES$_{\text{Corr}}$ extracted from NT and HM, respectively. Results are reported in means ± 95% CI.

Results

For performance, HM (0.27 ± 0.02) was statistically greater than NT (0.17 ±0.02). The only two HM models that were statistically greater than NT were LHTH and LLTH. The ES$_{\text{WM}}$ ± 95% CI for LHTH and LLTH were 0.38 ± 0.27 and 0.37 ± 0.09, respectively. For VO$_{2\text{max}}$, the only HM model that was statistically greater than NT was LLTH (0.37 ± 0.12). For [Hb], the only HM model that was statistically greater than NT was LHTH (0.53 ± 0.27). There were no significant differences between groups for Hct. As a whole, in the HM group, there was a significant correlation between the ES$_{\text{Corr}}$ for
VO₂max and performance ($r = 0.67, p = 0.00008$), however no significant correlation was observed between HM ES₉corr for [Hb] or Hct and VO₂max.

**Conclusion**

In conclusion, as a whole, HM is more beneficial to improving SL performance when compared to SL training alone. In addition, the greatest benefits from HM are from LHTH and LLTH. Further, the results of VO₂max, [Hb], and Hct between LHTH and LLTH are unclear. Therefore, it is still uncertain what factor(s) mediate the improved SL performance.

_______________________, Committee Chair
Daryl Parker, Ph.D.

_______________________
Date
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Chapter 1
INTRODUCTION

In 1968, Mexico City, Mexico hosted the XIX Summer Olympics Games. This was the first time the summer Olympic Games were held at an altitude ~2,200m (~7200 feet) above sea level (SL). Due to the altitude, the ability of the SL endurance athletes to perform was questioned (Robergs & Keteyian, 2003). At altitude there is a decrease in partial pressure of oxygen ($P_{O_2}$) which would effect oxygen delivery to the muscle and potentially sports performance. It is important to note that in endurance events (greater than 3000m) of the Mexico City Games, the performance results of those events were 6% slower than the world records (Pugh, 1969).

Prior to the 1968 Summer Olympic Games several studies were carried out to examine acclimatization as well as performance of athletes to altitudes similar to those of Mexico City. Balke, Nagle, and Daniels (1965) examined exercise responses to four subjects’ at 2300m above sea level. The authors observed performance in the one mile run decreased after two to three days of altitude exposure. After the 10 day study, performance in the one mile run of the subjects returned close to pre-altitude values (Balke et al., 1965). In a follow up study by Faulkner, Daniels, and Balke (1967) the authors investigated whether performance would return to pre-altitude values during 23 days of training at altitude. Faulkner at al. (1967) found similar results to Balke et al. (1965), but performance returned to pre-altitude values after two to three weeks of training at altitude.
A key finding in both studies (Balke et al., 1965, Faulkner et al., 1967) was that upon returning to SL from altitude training, the authors observed increases in exercise performance in the athletes. Questions were then posed whether training at altitude could be used synergistically to improve SL performance. Following the 1968 Olympic Games increased interests in the positive effects of altitude training lead to numerous studies on this topic.

A review by Bailey and Davies (1997) found little evidence to support altitude training for improvement of SL performance. The author’s cited many disadvantages to altitude training which include decreases in cardiac output, blood flow, and training intensity (Bailey & Davies, 1997). Several models of altitude training or hypoxic manipulation (HM) have evolved to combat the disadvantages cited by Bailey and Davies (1997). The HM models include: 1) Live High + Train High (LHTH) 2) Live high + Train low (LHTL) 3) Live low + Train high (LLTH) and 4) intermittent hypoxic exposure (IHE). Hypoxic exposure can be administered by either hypobaric hypoxia or normobaric hypoxia. Hypobaric hypoxia can be achieved by ascending to altitude or by use of a hypobaric chamber, while normobaric hypoxia can be achieved by use of nitrogen dilution or oxygen filtration (Wilber 2007).

Studies in the past decades investigating the possible increase in benefits of HM on SL performance have provided conflicting results. Levine and Stray-Gundersen (1997) investigated the effects of LHTL on running performance. The results of their study showed an increase in 5,000m time trial (TT) in the LHTL group while no improvements in performance were observed in the control group (CG). However,
Aughey et al. (2005) observed no changes in total work output in cyclists after 23 days of LHTL. An investigation on LHTH by Burtscher, Nachbauer, Baumgartl, and Philadelphia (1996), reported an increase in total work capacity (TWC) and VO₂max in the LHTH group. In contrast to the findings of increase in TWC observed by Burtscher et al. (1996), Buskirk, Kollias, Akers, Prokop, and Reategui (1967) observed no improvement in performance under LHTH exercise conditions upon returning to sea level. Meeuwsen, Hendriksen, and Holewijn (2001) examined the effects of LLTH on 16 tri-athletes using a cycle ergometer. They reported an increase in peak power output (PPO) during a maximal exercise test. While Roels, Bentley, Coste, Mercier, and Millet (2007) also examined the effects of LLTH on athletes but found LLTH had no effect on SL performance. The results of Roels et al. (2007) showed increases in PPO for both the CG and LLTH group, but no differences were found between the two groups. A study by Katayama, Matsuo, Ishida, Mori, and Miyamura (2003) observed the effects of IHE on exercise performance. They observed improvements in 3000mTT and running time to exhaustion in the IHE group. A similar study by Julian et al. (2004) found no significant differences in exercise performance between the IHE and control groups.

Because of the conflicting results of HM studies there is still no clear evidence for the inclusion of HM into training programs. The use of a meta-analysis on HM data may help to resolve the question whether it will improve SL performance. The meta-analytic technique is an effective means of combining conflicting data to resolve equivocal outcomes. Previously, Bonetti and Hopkins (2009) used this technique to determine the
effects hypoxia would have on SL performance. However, there may be limitations to the method in which they estimated effect size (ES).

In summary, the findings of studies (Balke et al., 1965; Faulkner et al., 1967) conducted prior to the 1968 Summer Olympic Games on acclimatization to moderate altitude generated an increased interest on HM to improve SL performance. This has lead to multiple studies conducted on possible benefits of HM for improving SL performance. However, the results on HM studies are conflicting. By utilizing a meta-analysis and calculating the ES of HM data, the effect of HM may be resolved.

Purpose of Study

The purpose of this study was to conduct a meta-analysis on HM studies to identify the effects of HM versus normoxic training (NT) on SL exercise performance, VO₂max, hematocrit (Hct) and hemoglobin concentration [Hb] in trained athletes.

Significance of Study

Numerous amount of research has investigated the effects of exercise and hypoxia. However, with conflicting results on HM studies there was still no clear understanding of the effects hypoxia and exercise has not only on performance but the underlying physiological adaptations. Acute and chronic adaptations to continuous exposure to altitude have been well documented. However, the adaptations that occur from combining both exercise and hypoxia are still uncertain. In addition, it is not well understood if hypoxia works synergistically with exercise. From the results of this meta-analysis, a better understanding of how both exercise and hypoxia can effect the human physiology can be understood.
Assumptions

1. The methods and procedures of the journal articles that are included in this study were correct and properly followed by the researchers.

2. The researchers of the experimental studies used the appropriate statistical analyses to analyze their data.

Limitations to Meta-analysis (Rhea, 2004b)

1. Only the studies meeting the inclusion criteria for this analysis were analyzed.

2. This meta-analysis combined results from multiple HM studies utilizing different experimental research designs. Referred to as comparing “apples to oranges”.

3. The results of the study only apply to trained athletes.

4. Studies utilizing animal models or untrained human subjects were not included in the analysis.

5. By using the key words such as altitude, training, hypoxic/hypoxia and performance, the literature search may be limited on finding articles pertaining to this meta-analysis.

Delimitations to Meta-analysis (Rhea, 2004b)

1. By combining multiple ES’s on HM, a more accurate conclusion would be drawn on its effectiveness on sea level performance.

2. The inclusion criteria designed for this study included journal articles that are pertinent to HM. A pertinent journal article was one that uses an HM model that reports performance, VO$_2$max, Hct, and [Hb] results on trained athletes.
3. Since the results of the experimental studies are represented in means and standard deviations, those results are scaled to the same unit. Since they are scaled to the same unit, one can compare multiple results of different research designs as long as they have the same underlying topic (HM).

Definition of Terms

Erythropoietin is a hormone that is released from the kidney’s that stimulates the production of red blood cell (RBC).

Hypoxia is a decrease in oxygen (O2) availability resulting from decrease in P_{O2}.

IHE or intermittent hypoxic exposure is intermittent exposure to high altitude (≥ 3000m). Subjects are exposed to either continuous intermittent (I_C) or hypoxic to normoxic ratio (I_R). For I_C, subjects spend short duration of time (maximum 3 hours) continuously in hypoxic environment per day. For I_R, subjects are exposed intermittently to hypoxia followed by normoxia, sometimes in a five minute on five minute off hypoxia to normoxia ratio. Exercise training was is only performed in normoxia.

LLTH is living at low altitude (<1200m) and training at moderate to high altitude (2300-3200m). In this HM model exercise training is only performed in a hypoxic environment, while a person lives at low altitude.

LHTH is living and training at moderate altitude (>1700m). In this HM model, persons are continuously living and training at altitude. At no point during the training camp does the person go to low or SL altitude.
LHTL is living at moderate to high altitude (1700m – 3500m) but training at low altitude (<1200m). The persons will either at altitude or in an hypoxic environment but only train at or near SL. Duration of hypoxic exposure is ≥ 8 hours per day.

Partial pressure (PO2) is the pressure of a specific gas for a given volume of space. VO2 is the volume of oxygen consumed by the body to produce energy, usually represented in absolute (L/min) or relative terms (ml/kg/min).

Research Questions

1. Does HM improve sea level performance greater than NT?

2. If HM is more effective than NT, do the various models differ from one another?

3. What effect does HM have on VO2max, Hct, and [Hb]?
The purpose of this meta-analysis on HM studies was to identify its effectiveness on improving SL performance in trained endurance athletes. Therefore, this chapter reviewed the conflicting results of HM studies on SL performance. In this chapter, the HM models which include LHTH, LHTL, LLTH and IHE will be discussed. Each HM model will be defined by describing specific details of a study and reporting performance results of their study and other similar studies. Also, the mechanism(s) of HM and the advantages of using a meta-analytical technique were included in this chapter.

Living High Training High

The classic altitude training model is LHTH. Early studies on LHTH investigated the acclimatization and work capacity of athletes to moderate altitude (Turner, Hoffler, Billings and Bason, 1969). Interestingly Faulkner et al. (1967) found upon returning from altitude sojourn average work capacity was greater at SL.

Living high training high consists of living and training at moderate (~2300m) to high altitude (>4000m) (Buskirk et al., 1967). Faulkner et al. (1967) observed five well conditioned adult males for 14 days at a moderate altitude (2300m Alamosa, Colorado). Exercise training while at altitude consisted of either running or swimming a minimum of three miles per day. An incremental exercise test pre- and three and 21 days post-altitude was used to determine VO₂max and maximal workload on a bicycle ergometer. The authors observed a statistically higher work capacity on the bicycle ergometer post-
altitude (SL) versus pre-altitude at 1800kg-m/min (294W) and 1665kg-m/min (272W), respectively (Faulkner et al., 1967). These findings were consistent with those of Balke et al. (1965) who observed improvements in one mile run times after 10 days at the same altitude (2,300m Red River, NM). In contrast to their findings of increase in one mile run time and work capacity on a bicycle ergometer (Balke et al., 1965; Faulkner et al., 1967), Buskirk, Kollias, Akers, Prokop, and Reategui (1967) found no improvement in running performance in six well conditioned runners. The subjects were divided into two groups with three subjects per group. One group of subjects spent 63 days living and training at Nunoa, Peru (4000m). The other group also stayed at Nunoa, Peru, however, after 48 days was moved to Mt. Evans then to Alamosa, Colorado (4300 and 2300m, respectively). Difference between the studies by Buskirk et al. (1967) and those of Balke et al. (1965) and Faulkner et al. (1967) was the elevation of altitude and total exposure time to the hypobaric hypoxic conditions. Balke et al. (1965) and Faulkner et al. (1967) studied healthy male athletes at 10 and 14 days at an altitude of 2300m while Buskirk et al. (1967) studied athletes at an altitude and exposure time of 2,300m to 4,300m for 63 days. The high altitude and increased exposure time may have reduced training intensity causing detraining which may contribute to the decrement in performance of the six athletes during SL exercise testing (Buskirk et al. 1967).

Bailey et al. (1998) investigated the effects of LHTH in two separate studies to test sub maximal and maximal exercise performance. For the sub-maximal exercise training study, at SL the researchers observed increases in sub-maximal running speeds of 9% and 12% at lactate concentrations of 2 and 4mmol, respectively (Albuquerque,
New Mexico 1500-2000). The improvement in performance was only observed in the
LHTH group. In the maximal exercise test study, the subjects in the LHTH group showed
a decrement in performance by increasing running speed by .13m/s (Bailey et al., 1998).
Levine and Stray-Gundersen (1997), observed no improvement in 5,000mTT after three
weeks of LHTH at Deer Valley, Utah. In contrast to the results of Levine and Stray-
Gundersen (1997), Burtscher, Nachbauer, Baumgartl, and Philadelphia (1996) reported
that after 12 days of LHTH at similar altitudes a 16% increase in TWC on a bicycle
ergometer was observed. These results of increase work capacity were similar to those of
prior studies (Faulkner et al., 1967). In conclusion, results from LHTH studies are still
conflicting and may be attributed to reduction in training intensity at high altitudes,
thereby causing detraining. Therefore, another HM model was created to combat the
detraining that accompanies LHTH.

Living High Training Low

Living high training low is an HM model where a person lives at moderate
altitude and trains at low altitude (Levine & Stray-Gundersen, 1997). Training at altitude
has shown to decrease exercise intensity which may cause detraining and affect sea-level
performance of athletes (Buskirk et al., 1967). Levine and Stray-Gundersen introduced
the LHTL altitude training model to combat the detraining that accompanies LHTH
(Levine & Stray-Gundersen, 1997). The benefit of this HM model was athletes would
live at moderate altitude and gain the physiological adaptations that accompany
acclimatization to altitude but are still be able to maintain exercise intensity by training at
a low altitude.
Levine and Stray-Gundersen (1997) studied the effects of four weeks of LHTL on male and female competitive runners. Prior to the study subjects were brought to Dallas, Texas (150m) for familiarization of all exercise tests. Four weeks prior to the study, the subjects participated in a four week training program to insure the subjects were well conditioned before participating in any altitude treatment. Subjects were divided into a control group (CG or SL), LHTL or LHTH group. The CG lived and trained at the US Olympic Training Center in Chula Vista, California (150m). The LHTH group lived and trained at Deer Valley, Utah (2500m) while the LHTL lived at Deer Valley, Utah, but trained at Salt Lake City, Utah (1250m). From their results the authors reported that LHTL group improved 5,000mTT by 13.4 ± 10 seconds upon returning to sea-level. The improvements in performance were significantly greater than the CG and LHTH groups (Levine & Stray-Gundersen, 1997). A similar study using elite male and female runners Stray-Gundersen, Chapman, and Levine (2001) observed a 5.8 second (1.1%) improvement in 3,000mTT. These results supported their previous findings. A limitation of this study was the use of no CG which does not allow for direct comparison. In another study with no CG, Wehrlin, Zuest, Hallen, and Marti (2006) also observed an increase in performance time to exhaustion (TE) by 41 seconds in a GXT. A 3.7% improvement in mean power output has also been observed in cyclists following LHTL (Roberts et al. 2003). In contrast to Levine and Stray-Gundersen (1997) and Stray-Gundersen et al.(2001), Robach et al. (2006) demonstrated after 13 days of simulated LHTL (2,500-3,000m) there were no significant increase 2,000mTT in highly trained swimmers. Clark et al. (2003) support the findings of Robach et al. (2006) when they reported no
significant differences in PPO on a cycle ergometer between LHTL and CG after 9-10 hours of simulated altitude for 20 nights.

Some studies have reported improvements in sub maximal exercise performance following LHTL model (Gore et al., 2001; Schmitt et al., 2006). Gore et al. (2001) investigated the effects of LHTL for 23 nights at a simulated altitude of 3,000m. The subjects were exposed to simulated altitude using a nitrogen rich room for 9.5 hours. The authors reported that sub-maximal efficiency was significantly improved by 0.8% in the LHTL group. Schmitt et al. (2006) found similar results, but examined VO2 and power output at respiratory compensation point (VO2RCP and P RCP) instead of efficiency. In this study the HM group was exposed to a hypobaric hypoxic environment of 2500-3500m. The authors reported a significant increase PPO as well as in VO2RCP and P RCP for LHTL versus CG.

In conclusion, evidence on whether LHTL improves SL performance over NT remains inconclusive and therefore no clear conclusion can be drawn. Furthermore, access to suitable geography and terrain to reside at maybe difficult for most people. Therefore, other HM models were designed to decrease the duration of hypoxic exposure.

Living Low Training High

Living low training high is an HM model were a person lives at low altitude but trains at moderate altitude. The implementation of LLTH maybe more suitable model than the previous HM models discussed. In the LLTH model, subjects are not subjected to long (≥ 8 hours per day) but rather short (≤ 2 hours per day) durations of hypoxic conditions. This is a geographically advantage. For instance, access to moderate altitude
terrains is not necessarily needed. However, this HM model is different in that exercise training is performed only in hypoxic conditions. Research suggests altitude exposure plus exercise training may work synergistically to induce the adaptations necessary for increase in SL performance (Meeuwsen et al. 2001).

Meeuwsen et al. (2001) performed a 10 day study on LLTH in eight male tri-athletes. Sixteen subjects were divided into either the HM or CG. Exercise was performed on cycle ergometer 2hrs/day in a hypobaric chamber at either 2,500m or SL. The intensity of the training was set at 60-70% of each subject’s heart rate reserve. Following the intervention the researchers reported a 7.4% and 5% increase in peak aerobic and peak anaerobic power in the HM group while no significant increases in power were observed for the CG. Meeuwsen et al. (2001) results were further supported by Hendriksen and Meeuwsen (2003) when they reported a 5.2% and 3.8% increase in peak aerobic and peak anaerobic power following nine days of LLTH. The authors also observed a significant 3.7% increase in peak aerobic power two days after the study in the control group. These two studies were part of a cross-over research design that was performed one year apart (Hendriksen & Meeuwsen, 2003; Meeuwsen et al., 2001). Further support for increase in performance work capacity over normoxic training using the LLTH model was observed by Loeppky and Bynum (1970) reported LLTH had 65% improvement in work capacity over CG (139 seconds LLTH vs. 49 seconds CG) during a treadmill running test. Terrados, Melichna, Sylven, Jansson, and Kaijser (1988) also observed a significant 33% increase in TWC compared to a non-significant 22% increase in the CG.
Roels et al. (2007) and Roels et al. (2005) investigated high intensity interval training (HIIT) using a breathing mask to simulate an altitude of 3,000m. The results of the study indicated both LLTH and CG increased performance but there were no statistical differences between the two groups (Roels et al., 2007; Roels et al., 2005). The authors concluded that HIIT either at altitude or sea-level increased performance equally. Further, Morton and Cable (2005) observed similar improvements in performance following 4 weeks of interval training at a simulated altitude of 2750m for 30 minutes a day, three times a week.

To conclude, several studies have reported both significant and non-significant improvements following LLTH. The contradicting results from these studies do not allow for a clear conclusion as to the effectiveness of LLTH for improving SL performance over SL training alone.

**Intermittent Hypoxic Exposure**

Intermittent hypoxic exposure is a HM model where a person is intermittently exposed to a simulated altitude at rest by use of a breathing mask, hypobaric chamber or a normobaric hypoxic room/tent. An advantage to IHE is the use of these equipment which is ideal for persons who do not have access to moderate or high altitude environments. Another advantage is that minimal time is required to implement this method of HM. This method requires exposure to short durations of hypoxia that are similar to high altitude which decreases the time needed to potentially improve SL performance. Research suggests intermittent exposure to high altitudes can stimulate
increase in EPO production (Knaupp, Khilnani, Sherwood, & Steinberg, 1992) that may be advantageous to improving SL performance.

Julian et al. (2004) studied the effects of IHE on SL exercise performance. For four weeks, subjects were asked to breathe into a mask that either had hypoxic or normoxic air. The HM group was exposed to the hypoxic air five times a week using a five minutes on five minutes off ratio for 70 minutes while the control group followed the same procedures while breathing normal air. Unfortunately, the authors did not report the simulated altitude at which the subjects were exposed. Subjects in both groups were unaware of which treatment they received throughout the study. All subjects participated in the same outside exercise training program which consisted of moderate to high intensity running. Upon completion of the study the authors reported no significant difference between the 3,000mTT in the HM or CG (Julian et al. 2004).

Rodriguez et al. (2007) also examined the effects of IHE to SL performance. Instead of normobaric hypoxic exposure previously used by Julian et al. (2004), Rodriguez et al. (2007) used a hypobaric chamber with simulated altitude of 4,000 to 5,500m and at a continuous duration of 3hrs/day for 5 days for a total of four weeks. Even with differences in exposure time and method of exposure, no improvements in time trial performance were observed for the runners and swimmers in either the HM or CG. Tadibi, Dehnert, Menold and Bartsch (2007) investigated the effects of IHE on endurance trained subjects using a cycle ergometer. They reported no improvements in PPO during a maximal exercise test or Wingate exercise test.
Katayama et al. (2003) also investigated IHE and found conflicting results to those of Julian et al. (2004) and Rodriguez et al. (2007). The authors observed lower VO$_2$ for a given incline during sub-maximal exercise as well as increases in 3000mTT and running time to exhaustion (Katayama et al., 2003). In their study, Katayama et al. (2003) exposed subjects to a simulated altitude of 4,500m continuously for 120 minutes 3 times a week for 3 weeks. Similar improvements to running time to exhaustion were observed by Katayama, Sato, Matsuo, Ishida, Iwasaki, and Miyamura (2004).

In conclusion, numerous studies using various methods and durations of intermittent exposure have provided conflicting results. Some studies have reported improvements in SL performance while others have not. Therefore, it is still uncertain as to the effectiveness of IHE.

**Mechanism(s) of Hypoxic Manipulation**

Upon exposure to altitude, acute and chronic adaptations occur to combat the effects of the hypoxic environment. A chronic adaptation to hypoxia is an increase in erythropoietin (EPO) which in turn causes an increase in red blood cell (RBC) (Elliott, Pham, & Macdougall, 2008). Increases RBC’s allows for an increase in O$_2$ carrying capacity. Recently, it was demonstrated that under normoxic exercise conditions, administration of rHuEPO increased aerobic power by 5.4% to 7.9% in healthy male subjects (Lundby, Achman-Andersen, Thomsen, Norgaard, & Robach, 2008). Since a chronic adaptation to hypoxia is an increase in EPO thereby increasing RBC, it suggests HM has the potential to improve SL performance. As previously reported a 13.4 ± 10 seconds improvement in 5,000mTT was attributed to increase in 5% VO$_2$max (Levine &
Stray-Gundersen, 1997). The 5% increase in VO$_2$max was attributed to a 9% increase of red cell mass volume (RCV) in LHTL (Levine & Stray-Gundersen 1997). Further, Wehrlein et al. (2006) observed a 5.3% and 5% increase in hemoglobin and RCV, respectively with a 4.1% increase in VO$_2$max.

Recently the theory that VO$_2$max is the mechanism for improvement in SL performance has been questioned (Gore et al., 2007). A study reported increases in EPO after 120 minutes of continuous or 240 minutes intermittent exposure to simulated altitude of 10.5% PO$_2$ (Knaupp et al. 1992) while another study reported no increase erythropoietin, RCV, and hemoglobin (Gore et al., 2006). Contrary to the findings of Levine and Stray-Gundersen (1997) increases in performance have been reported without increases in VO$_2$max (Roberts et al. 2003). This leads to the question whether other physiological adaptations from hypoxic exposure may occur other than those of increase in RCV and VO$_2$max. A review by Gore et al. (2007) presented other possible mechanisms for improvement SL performance other than those previously reported by others. Gore et al. (2007) summarized that the adaptation from LHTL occurs in the mitochondria which improves efficiency and muscle buffering capacity. To support this alternate theory, Katayama et al. (2003) observed an increase in sub-maximal exercise efficiency after three weeks of IHE, while Schmitt et al. (2006) observed an increase in cycling economy and PPO during 12-18 nights of LHTL. Further, in a preliminary study Parker, Salgado, Quintana, and Faria (2009) reported variables that contribute to maximal power ($W_{\text{max}}$) during a GXT on a cycle ergometer. The largest contribution to $W_{\text{max}}$ was
VO$_2$RCP, followed by VO$_2$max, and finally economy. Their findings suggest a sub-maximal not a maximal variable provides a greater contribution to performance.

To conclude, the primary mechanism for HM to improve SL performance is believed to be VO$_2$max. However, increasing results from other studies suggest other possible mechanism. Therefore, the mechanism for improving SL performance is not well understood.

Meta-analysis

A meta-analysis is a method of performing a review of research studies (Rhea, 2004b). It is an extensive review of literature that uses specific procedures (Thomas and French, 1986) to quantify results from other experimental studies by calculating ES (Noar 2006). There are advantages to conducting a meta-analysis versus a traditional review of research studies. In a meta-analysis, inclusion criteria are developed to insure minimal biasness from the researcher. While in a traditional review, no clear inclusion criteria are developed which allows for a more subjective method of determining which journal articles are include (Rhea, 2004a).

By utilizing a meta-analytical technique, the ES from numerous studies can be calculated and combined for analysis (Rhea, 2004a). The calculation of an ES can determine the effectiveness of a treatment. This is also an advantage of meta-analysis over traditional reviews. Often times in traditional reviews, results of a treatment are considered non-effective because it does not reach a certain significance level (p-value). However, p-value can be effected by sample size (Rhea, 2004b). A small sample size in a research study may not have enough power to show statistical significance. Further, the
p–value determines the probability of the outcome of the results but does not describe the effectiveness of the treatment (Rhea, 2004a). The ES of a treatment can be determined whether it is small, moderate or large (Rhea, 2004a). The meta-analytical technique has be utilized to determine dose response relationships in strength training for individuals who are untrained, trained and athletes (Rhea, Alvar, Burkett, & Ball, 2003; Peterson, Rhea & Alvar, 2004). Recently, the meta-analytical technique was utilized to determine the dose response relationship of duration and volume for tapering in endurance athletes (Bosquet, Montpetit, Arvisais & Mujika 2007).

**Conclusion**

In summary the results of effectiveness of HM are conflicting. There is no clear evidence to support that HM as a whole or any one model will have a greater effect on sea-level performance over normoxic training. Multiple studies described above using different HM models have reported varying performance results as well as different theories for mechanistic adaptations. A meta-analysis is a research review method that can be used to combine HM data and reconcile the equivocal nature of this data. This method has been used to help quantify other research studies and help to answer other research questions.
Chapter 3

METHODOLOGY

The purpose of this analysis was to determine the effects HM would have on SL performance, VO₂max, Hct, and [Hb]. For an accurate analysis on HM studies, meta-analytical procedures were followed to determine the effects of HM. In this section, the procedures such as the journal article selection, data extraction, and the data analyses were discussed.

Journal Article Selection

In the process of selecting pertinent journal articles on HM studies, the authors searched for published peer-reviewed journal articles from 1965 to 2008. The online databases such as SpringerLink, ScienceDirect (Elsevier), ERIC and PubMed were used to locate relevant studies on HM. For the online database search, key words such as altitude, training, hypoxic/hypoxia and performance were used. Further, to expand the literature search, the reference lists of peer-review journal articles were reviewed to find pertinent HM studies.

An inclusion criteria was developed to determine which journal articles were to be included in this analysis. Studies included in the meta-analysis met the following inclusion criteria: 1) adequate use of control group in the research design 2) published performance, or VO₂max, or [Hb], or Hct results that report means and standard deviations (SD) and 3) use of trained athletes. If standard error was reported rather than SD, the SD was calculated using the following formula:
\[ SD = SE \times \sqrt{N} \] (Vincent, 2005)

where; SE was the reported standard error, and N was the sample size of the group. If inclusion criteria were met, the journal articles were read and coded (Thomas & French, 1986) for the following variables: 1) HM model which include LHTH, LHTL, LLTH and IHE, 2) Performance which were defined as time in a TT (or time to exhaustion), or PPO during a GXT or TWC, and 3) VO₂\(_{\text{max}}\) as well as hematological variables which included Hct and [Hb]. In the case of the performance variables, if more than one variable were measured in the HM study, only one was included in the analysis with the primary variable being time in a TT followed by PPO then TWC. This allowed for only one measurement of performance variable to be included in the analysis. Upon completion of the literature search, 74 HM studies were found of which 29, 27, 18, and 14 of those studies met the inclusion criteria for performance, VO₂\(_{\text{max}}\), [Hb], and Hct, respectively.

Data Extraction

Prior to calculating ES from individual HM studies, they were grouped into the NT or HM group. For further analyses, journal articles were further grouped into LHTH, LHTL, LLTH, or IHE groups. After grouping studies into their respective HM groups, the ES were extracted from the studies. To determine the effectiveness of HM on SL performance, ES from each study for the different variables were calculated. The ES was calculated using the following formula:

\[ \text{Cohen’s } d = \frac{(\text{Post}_m - \text{Pre}_m)}{\text{PreSD}} \] (Rhea, 2004a)
where; Postₘ was the post-test mean, Preₘ was the pre-test mean, and Preₜ was the pre-test SD. A total of 42 and 49 performance ES’s were extracted from the NT and HM groups, respectively. There were a total of 39 and 39 VO₂max ES’s extracted from NT and HM groups, respectively. For each group, 23 ES’s of Hb were extracted from NT and HM. A total of 15 and 17 ES’s were extracted for Hct from NT and HM groups, respectively. Table 1 summarizes the number of performance ES variables as well as the total ES for each HM model. Table 3 summarizes the number of ES for VO₂max, [Hb], and Hct from the NT and HM groups.

Data Analyses

Once all ES were calculated using Cohen’s d formula, they were corrected for small sample biasness. Thomas and French (1986) reported that small sample sizes (n < 20) have a positive biasness; therefore, all ES’s for this current analysis were corrected using the correction factor. The following formula was used to determine the correction factor:

\[
\text{Correction factor} = 1 - \frac{3}{4m-1}
\]

(Thomas & French, 1986)

where; m is the sample size. Since the correction factor varied based on sample size, a correction factor was calculated for each ES. The correction factor was then multiplied by the ES to give an ES corrected for sample size (EScorr). The EScorr were further standardized by calculating the weighted mean ES (ESWM) for each individual HM model for performance, VO₂max, Hct, and [Hb]. The ESWM was calculated by dividing the EScorr over the reciprocal of the variance of the corrected ES (EScorr var) (Thomas & French, 1986). The following formula was used to determine EScorr var:
ES_{corr \text{ Var}} = ((SS + SS)/(SS \times SS)) + ((ES_{corr} \times ES_{corr})/(2 \times (SS + SS)) \quad (Thomas \ & French, 1986)

where; SS was the sample size and ES_{corr} was ES corrected for sample size. To calculate the ES_{WM} for each individual HM model for performance, VO_2max, Hct, and [Hb] the following formula were used:

$$ES_{WM} = \sum (ES_{corr} / ES_{corr \text{ Var}}) / \sum (1/ES_{corr \text{ Var}}) \quad (Thomas \ & French, 1986)$$

where; ES_{corr} was the ES corrected for sample size and ES_{corr \text{ Var}} of the corrected ES. By determining the ES_{WM}, it gives a true representation of the ES as it accounts for the variance of each ES. What this means is that ES with smaller variance will be weighted more than ES with large variances. The outcome will be an ES_{WM} that was standardized by the variance. Before statistically analysis were conducted each ES_{corr} where tested for homogeneity using the following formula:

$$\text{Homogeneity} \pm 2 \text{ SE (H}_2\text{SE)} = ES_{corr} \pm (SE_{ES \text{ corr}})$$

where; ES_{corr} was the ES corrected for sample size and SE_{ES corr} was the standard error of the ES corrected for sample size or the $\sqrt{ES_{corr \text{ Var}}}$. The ES was considered to not be homogenous with the other ES_{corr} if the ES_{WM} did not fall within $H^2\text{SE}$ thus excluding it from the analysis. For NT and LHTL groups, one [Hb] ES_{corr} for each model were not included as well as one VO_2max ES_{corr} for LHTL. For LHTH, one ES_{corr} for VO_2max and [Hb] were excluded from the analysis. For LLTH, one ES_{corr} for both [Hb] and Hct were not included, while no ES_{corr} were excluded for IHE.

For statistical analysis the 95% CI were calculated for each ES_{WM}. The 95% CI were compared between HM models of the varying variables. If any 95% CI overlapped
each other, they were considered not statistically different between each other. Further, if the 95% CI overlapped zero they were considered not statistically different from zero, thus meaning there was no statistical change. Pearson correlation (Microsoft Excel 2007) was used to determine relationship between the $ES_{Corr}$ for HM on VO$_{2\text{max}}$ and performance, VO$_{2\text{max}}$ and [Hb] and VO$_{2\text{max}}$ and Hct. The alpha level was set at $p \leq 0.05$. Unless stated otherwise, all results were reported in $ES_{WM} \pm 95\%$ CI.
Chapter 4

RESULTS

Hypoxic Manipulation versus Normoxic Training

The primary question of this investigation was to determine if HM would provide a greater effect for improving SL performance over NT alone. Figure 1 illustrates as a whole, $ES_{WM}$ for HM was statistically greater than NT. The $ES_{WM} \pm 95\% \ CI$ were $0.17 \pm 0.02$ and $0.27 \pm 0.02$ for NT and HM, respectively. Also, both NT and HM were significantly greater than zero (Figure 1).

Performance between the Four Hypoxic Manipulation Models

Since a significant result was observed for HM, the various models of HM training were examined to determine if one model provided a greater benefit than another. The largest $ES_{WM}$ for performance was LHTH followed by LLTH, than LHTL, and finally IHE (Figure 2). LHTH was significantly greater than NT and zero, however, it was not significantly greater than LHTL, LLTH, or IHE. LLTH was significantly greater than NT, IHE, or zero; however, it was not significantly greater than LHTH or LHTL. LHTL was significantly greater than zero, but was not significantly greater than NT, LHTH, LLTH, or IHE (Figure 2). IHE was significantly greater than zero, however was not significantly greater than NT, LHTL, or LHTH (Figure 2). The $ES_{WM} \pm 95\% \ CI$ for performance of LHTL, LHTH, LLTH, and IHE were $0.24 \pm 0.09$, $0.38 \pm 0.17$, $0.37 \pm 0.09$, and $0.17 \pm 0.06$, respectively. Table 2 summarizes the mean ± SD for performance.
Comparison of VO2max between Groups

The postulated effect for improvements with HM training have been an improvement in VO2max. Since some models improved SL performance better than others, the corresponding VO2max for each HM models was examined to determine if this physiological variable would explain the performance effect. For all HM models including NT, they were significantly greater than zero. The largest ESWM was from LLTH, followed by LHTH, than IHE, and finally LHTL (Figure 3). LLTH was the only HM model that was statistically greater than NT, but was not statistically greater than LHTL, LHTH, or IHE (Figure 3). LHTL, LHTH, or IHE were not statistically greater than NT (Figure 3). The ESWM ± 95% CI for NT, LHTL, LHTH, LLTH, and IHE was 0.20 ± 0.03, 0.28 ± 0.10, 0.32 ± 0.19, 0.37 ± 0.12, and 0.22 ± 0.11, respectively. There was a positive significant relationship between the ESCorr for VO2max and performance from HM (r = 0.67, p = 0.00008) (Figure 4).

Comparison of Hemoglobin and Hematocrit Between Groups

Since VO2max responses varied between the HM models, Hct and [Hb] was examined to determine there effects on VO2max. The largest and only statistically greater ESWM for [Hb] when compared to NT, LLTH, IHE, or zero was LHTH (Figure 5), although, it was not statistically greater than LHTL (Figure 5). LHTL, LLTH, or IHE were not statistically greater than NT or zero (Figure 5). The ESWM ± 95% CI for NT, LHTL, LHTH, LLTH, and IHE were 0.13 ± 0.05, 0.02 ± 0.31, 0.53 ± 0.27, -0.06 ± 0.21, and 0.01 ± 0.16, respectively. There was negative but non-significant relationship (r = -0.20, p = 0.48) between the ESCorr for VO2max and [Hb] from the HM (Figure 7).
The analysis of Hct only included ES_{WM} of four groups, which were NT, LHTL, LLTH, and IHE. No ES_{WM} was calculated from LHTH. All four groups were not statistically different between groups or zero (Figure 6). The ES_{WM} for NT, LHTL, LLTH, and IHE were 0.06 ± 0.08, 0.02 ± 0.31, -0.16 ± 0.21, and -0.08 ± 0.20, respectively. There was a positive but non-significant relationship (r = 0.43, p = 0.14) between the ESCorrVO_{2max} and Hct (Figure 8).
Table 1

The Number of Performance Effect Sizes from HM Models

<table>
<thead>
<tr>
<th>HM Model</th>
<th>TT</th>
<th>TWC</th>
<th>PP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHTL</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>LHTH</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>LLTH</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>IHE</td>
<td>14</td>
<td>0</td>
<td>4</td>
<td>18</td>
</tr>
</tbody>
</table>

Note. TT indicates time in a time trial or time to exhaustion, TWC indicates total work capacity, PP indicates peak power.
Table 2

Weighted Mean Effect Size for Performance

<table>
<thead>
<tr>
<th>HM Model</th>
<th>ES\textsubscript{WM}</th>
<th>± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT</td>
<td>0.17</td>
<td>0.08</td>
</tr>
<tr>
<td>LHTL</td>
<td>0.24</td>
<td>0.14</td>
</tr>
<tr>
<td>LHTH</td>
<td>0.38</td>
<td>0.18*</td>
</tr>
<tr>
<td>LLTH</td>
<td>0.37</td>
<td>0.15*</td>
</tr>
<tr>
<td>IHE</td>
<td>0.17</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Note. ES\textsubscript{WM} indicates the weighted mean effect size. (*) Indicates statistically greater than NT.
Table 3

ESWM for VO2max, [Hb], and Hct for each HM Model

<table>
<thead>
<tr>
<th></th>
<th>Number of ES</th>
<th>ESWM (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VO2max</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>39</td>
<td>0.2 (0.08)</td>
</tr>
<tr>
<td>LHTL</td>
<td>12</td>
<td>0.15 (0.15)</td>
</tr>
<tr>
<td>LHTH</td>
<td>6</td>
<td>0.32 (0.18)</td>
</tr>
<tr>
<td>LLTH</td>
<td>10</td>
<td>0.37 (0.17)*</td>
</tr>
<tr>
<td>IHE</td>
<td>11</td>
<td>0.22 (0.16)</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>[Hb]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>23</td>
<td>0.13 (0.10)</td>
</tr>
<tr>
<td>LHTL</td>
<td>5</td>
<td>0.02 (0.25)</td>
</tr>
<tr>
<td>LHTH</td>
<td>5</td>
<td>0.53 (0.22)*</td>
</tr>
<tr>
<td>LLTH</td>
<td>8</td>
<td>0.04 (0.18)</td>
</tr>
<tr>
<td>IHE</td>
<td>7</td>
<td>0.01 (0.18)</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hct (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT</td>
<td>17</td>
<td>0.17 (0.13)</td>
</tr>
<tr>
<td>LHTL</td>
<td>5</td>
<td>0.02 (0.25)</td>
</tr>
<tr>
<td>LHTH</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>LLTH</td>
<td>7</td>
<td>-0.15 (0.19)</td>
</tr>
<tr>
<td>IHE</td>
<td>6</td>
<td>-0.08 (0.19)</td>
</tr>
</tbody>
</table>

Note. (–) indicates no Hematocrit effect size were calculated from LHTH. (*) Indicates statistically greater than NT.
Figure 1 Comparison of ES_{WM} ± 95% CI for performance between groups. (*) Indicates statistically greater than NT. (+) Indicates statistically greater than zero.
Performance Effect Size Comparison between Groups

Figure 2 Comparison of weighted mean effect size for performance between groups. Results are $ES_{WM} \pm 95\%$ CI. (*) Indicates significantly greater than NT. (+) Indicates significantly greater than zero. ($\alpha$) Indicates not significantly greater than LHTL, LLTH, or IHE. ($\beta$) Indicates significantly greater than IHE but not LHTH or LHTL. ($\gamma$) Indicates not significantly greater than NT, LHTH, LLTH, or IHE. ($\theta$) Indicates not significantly greater than NT, LHTL, or LHTH.

Figure 2 Comparison of weighted mean effect size for performance between groups. Results are $ES_{WM} \pm 95\%$ CI. (*) Indicates significantly greater than NT. (+) Indicates significantly greater than zero. ($\alpha$) Indicates not significantly greater than LHTL, LLTH, or IHE. ($\beta$) Indicates significantly greater than IHE but not LHTH or LHTL. ($\gamma$) Indicates not significantly greater than NT, LHTH, LLTH, or IHE. ($\theta$) Indicates not significantly greater than NT, LHTL, or LHTH.
VO₂max Effect Size Comparison between Groups

Figure 3 Comparison of weighted mean effect size of VO₂max between groups. Results are ESwm ± 95% CI. (*) Indicates significantly greater than NT. (+) Indicates significantly greater than zero. (α) Indicates not significantly greater than LHTL, LHTH, or IHE. (β) Indicates LTLH, LHTH, or IHE not significantly greater than NT.
Figure 4 Correlation of ES_{Cor} between VO_{2max} and performance from HM significantly correlated $p \leq 0.05$
Hemoglobin Effect Size Comparison between Groups

![Diagram showing effect size comparison](image)

Figure 5 Comparison of ES_{WM} for [Hb]. Results are ES_{WM} ±95% CI. (*) Indicates significantly greater than NT, LLTH, and IHE but not significantly greater than LHTL. (+) Indicates significantly greater than zero. (α) Indicates not significantly greater than zero.
Figure 6 Comparison of $E_{WM}$ for Hct between groups. No $E_{WM}$ was calculated for LHTH. Results are $E_{WM} \pm 95\%$ CI. (*) Indicates not significantly different between groups and not significantly greater than zero.
VO$_2$max versus Hemoglobin Concentration

Figure 7 Correlation of ES$_{corr}$ between VO$_2$max and [Hb] from HM not significantly related. $p \leq 0.05$. 

\[
y = -0.188x + 0.2822 \\
R^2 = 0.0417
\]
VO₂max versus Hematocrit

Figure 8 Correlation of ESCorr between VO₂max and Hematocrit from HM not significantly related. $p \leq 0.05$
Chapter 5
DISCUSSION

Numerous studies have been conducted on HM for improving SL performance. However, the results of those studies have been in equivocal. The purpose of this investigation was to resolve the conflicting data. Therefore, there was a need for a meta-analysis on HM studies. The primary focus of this meta-analysis was to determine the effectiveness of HM versus NT for improving SL performance. The secondary focus was to determine if VO$_2$max and hematological variables mediate these performance effects.

Hypoxic Manipulation versus Normoxic Training

The ES$_{WM}$ for HM was statistically greater than NT. The results comparing the ES$_{WM}$ of performance suggest 1.5x greater effect utilizing HM versus NT. Based on a magnitude of ES scale (trivial, small, moderate, or large ES) (Rhea, 2004a) an ES$_{WM}$ of 0.27 for HM was categorized as small, whereas an ES$_{WM}$ of 0.17 for NT is considered trivial. This means even with the use of HM, while greater than NT, SL performance improvements would be small. This is consistent with previous reports examining HM training. Hendriksen and Meeuwsen (2003) reported a 3.8% increase in PPO on a cycle ergometer. In addition, Truijens, Toussaint, Dow, and Levine (2003) reported a 1.7% increase in 400m TT in swimmers. Hopkins, Hawley, and Burke (1999) have reported that a minimum of 0.5% improvement in performance may be meaningful in trained athletes. This means the small ES observed from HM may potentially be meaningful.
Comparison of Performance between Hypoxic Manipulation Models

It was determined that as a whole, HM was more effective in improving SL performance. Therefore, to further investigate, analysis of the 95% CI of the $ES_{WM}$ performance were compared between the groups. The two HM models that were statistically greater than NT were LHTH and LLTH, while LHTL and IHE were not statistically greater than NT. This indicates among the four HM models, utilizing LHTH or LLTH would most likely provide the greatest improvements in SL exercise performance.

The disadvantage of traditional altitude training is that there is a decrease in partial pressure of inspired oxygen ($P_{1O2}$) as altitude increases. The decrease in $P_{1O2}$ decreases O$_2$ delivery to the muscle, consequently a decrease in performance (Buskirk et al, 1967). However, from these results, the performance $ES_{WM}$ for LHTH is significantly greater than the NT group. This could possibly be attributed to the duration of hypoxic exposure and or the elevation of hypoxia. On average, for the studies included in this analysis, the duration of exposure was ~19 days, with a range of 12 to 28 days. The average elevation was ~2020 m, with a range of 1740 m to 2500 m. Buskirk et al. (1967) investigated subjects at altitudes greater than 4000 m for durations greater than 62 days. It is therefore conceivable using the LHTH model with shorter duration as well as moderate altitude exposure may increase SL performance. Interestingly, for LHTH the two largest $ES_{corr}$ were from a 12 day study. However, when compared to studies with greater than 12 days of hypoxic exposure, the $ES_{corr}$ were smaller. What this means is that the effectiveness of LHTH can potentially be mediated by the dosage (duration and
elevation) of hypoxia. Therefore, it may be important to revisit the early studies that investigated the effects of LHTH on SL performance, re-design the studies adjusting for duration and elevation of altitude as well as including a CG.

The ES_{WM} for LLTH was also greater than the NT group. Dufour et al. (2006) and Meeuwsen et al. (2001) reported improvements in performance following LLTH. The difference between the other three HM models and LLTH is that in LLTH exercise training was performed in brief (varying durations of 90 minutes a week for three weeks to 840 minutes for 10 days) exposure to hypoxia equivalent to approximately 2700m. This suggests a combination of exercise training in hypoxia may be more beneficial than LHTL and IHE. The advantage of LLTH is that persons are exposed to short durations of hypoxia but seem to still receive SL performance enhancements, whereas, in the LHTL model long durations of hypoxic exposure is needed to observe increases in SL performance.

In a recent meta-analysis on HM studies by Bonetti and Hopkins (2009), the authors concluded the largest improvement to SL performance for sub elite athletes was from simulated brief LHTL (simulated moderate to high altitude for approximately 1.5 to 5 hours per day), simulated LHTL (8 to 18 hours of continuous exposure) and LLTH. For elite athletes, only natural LHTL showed improvements in SL performance. While in our results, LHTL was not statistically greater than NT, only LHTH and LLTH were. It is uncertain to the authors of this current analysis as to the disparity in the results between the two meta-analyses. However, we did not separate between elite and sub elite athletes because there would be too few HM studies to analyze. Further, our results suggest
LLTH may improve performance while Bonetti and Hopkins (2009) did not. This difference may be explained because we were unable to locate studies on LLTH using elite athletes. This is a plausible explanation as to why we observed LLTH to improve SL performance and Bonetti and Hopkins (2009) did not.

In this current meta-analysis, all ES’s were calculated using Cohen’s $d = (Post_m - Pre_m)/PreSD$ (Rhea, 2004a) formula which allows for standardization of performance variables from different studies (Rhea, 2004a). This method standardizes ES to the SD of the outcome variable. Similarly, Bonetti and Hopkins (2009) calculated percent change in performance by dividing the mean-post score by the mean-pre score for studies without CG and for studies with CG, the mean-post score/mean-pre score for HM group was divide by the mean-post score/mean-pre score of the CG. However, they further attempted to standardize change in TT performance to mean power output. For the studies in which percent change in TT were calculated, the percent change in TT was standardized by multiplying by a factor which they derived by the power-velocity relationship. Moreover, changes in TE were converted to change in power output using a correction factor derived from the power-duration relationship. Further, change in TE during a GXT was converted to peak power by multiplying the appropriate conversion factor (Bonetti & Hopkins, 2009). However, an accurate conversion to power is not likely as the power-velocity relationship is not a direct 1 to 1 ratio. Hawley, Myburgh, Noakes, and Dennis (1997) observed a linear relationship between PPO during cycling TT with 40km performance (Hawley, Myburgh, Noakes, & Dennis, 1997), but use of this relationship as a method for estimating improvements in performance may be inaccurate.
For example, in the study by Hawley et al. (1997) the authors reported a 5% increase in PPO with only a 2-3% improvement in 40km cycling TT. Bonetti and Hopkins (2009) assume a 5% increase in PPO is equivalent to 3% improvement in TT performance, when in actuality there is only a 2% improvement in TT performance. This may over-estimate or even under-estimate some of their effects is they assume a 2% change. This was further supported by Stepto, Hawley, Dennis, & Hopkin (1999) who reported that PP correlates with 40kmTT but the percent change in peak power did not correlate in cycling performance. Therefore, using the power-velocity relationship may over or under-estimate change in performance.

An additional disadvantage to Bonetti and Hopkins (2009) analyses was that in their meta-analysis they included studies without SL control groups. This would not allow them to make direct comparison between HM and CG. For example, based on their analysis it would be difficult to determine whether the observed improvement in SL performance were from HM or from training alone. Additionally, since they included studies without CG, in order to make a more accurate conclusion whether HM improves SL performance they would need to include studies only looking at SL training.

Comparison of VO₂max and Hematological Variables

To investigate factors that may potentially mediate improvements in SL performance, a comparison was made between VO₂max, [Hb] and Hct. Traditionally, LHTL and IHE have been reported to increase VO₂max. The predominant theory is that exposure to hypoxia signals physiological adaptations that increase the synthesis of RBC increasing VO₂max (Levine & Stray-Gundersen, 1997). However, this may not be the
case. An interesting finding was that the $ES_{WM}$ of $VO_2max$ for LLTH was statistically greater than the NT group. In a previous meta-analysis, Bonetti and Hopkins (2009) reported improvements in $VO_2max$ were likely for LHTH, possible for LLTH, and trivial for LHTL in sub-elite athletes. For elite athletes, $VO_2max$ was impaired and unclear for LHTH and LHTL groups, respectively. This means that $VO_2max$ improvements are more apparent for the LHTH and LLTH groups. The results of $VO_2max$ for this current analysis are comparable with those of Bonetti and Hopkins (2009) even though standardization of performance ES was different between the two analyses.

It has been well documented that an adaptation to chronic hypoxia is an increase in [Hb] (Calbet, Lundby, Koskolou, & Boushel, 2006; Strohl, 2008). However, there is conflicting data as to whether brief exposure (varying exposure of ~90 min/day, 3 times per week to ~22hrs/day for four weeks at altitudes of ~2300 to 4400m) to hypoxia induces the same response (Katayama et al. 2004; Levine & Stray-Gundersen 1997; Rodriguez et al. 2000). From the results of this analysis LHTL, LLTH, and IHE $ES_{WM}$ of [Hb] was not different from NT. However, the $ES_{WM}$ of [Hb] for LHTH was greater then NT. Bonetti and Hopkins (2009) also reported moderate increase in [Hb] for the LHTH group. However, due to limited studies with [Hb] results, they only analyzed [Hb] for LHTH and simulated brief LHTL groups. The finding of [Hb] during LHTH was not surprising due to the adaptations that accompany chronic exposure to hypoxia. However, what was surprising was that from this current meta-analysis, the $ES_{WM}$ for LHTL was not different then NT. For the journal articles included in this analysis, the average duration of exposure was approximately 12.6 hours for approximately 14.6 days at an
altitude of ~2500m to 3500m. The recommended dosage for LHTL to see increases in performance, VO$_2$max, and hematological values is ~22 hours a day for four weeks at an altitude ~2200-2300m above sea-level (Wilber, Stray-Gundersen, & Levine, 2007). The hypoxic dose from the HM studies included in this current analysis may not have been adequate. This may help to explain why the ES$_{WM}$ of Hb for LHTL was not different from the NT group.

In this current analysis, the ES$_{WM}$ from only four groups were compared (NT, LHTL, LLTH, and IHE). No ES’s for Hct were extracted from LHTH. The reason no ES were extracted from LHTH was that the studies included in this analysis did not examine Hct. Hematocrit was not statistically different between groups. These results are similar with other findings that Hct values were unchanged after LLTH and IHE (Katayama et al. 2003; Katayama et al. 2004; Morton et al. 2005). The ES$_{WM}$ of Hct for LHTL were not different then NT. Conversely, Basset et al. (2005) reported a significant increase (5.2%) in Hct following eight hours, two days consecutively for a three-week time span at a simulated altitude of 3636m. Concluding that Hct responses to HM is highly variable and probably not related to change in VO$_2$max and SL performance.

Mechanism for Improving Performance

It is still unclear as to the mechanism for improvement in performance. It is commonly believed that LHTL increases VO$_2$max by way of increases in [Hb] or Hct. However, from this analysis, the results revealed that improvements in performance were from LHTH and LLTH. It is difficult to draw a conclusion based on these results. In both groups, performance improved almost equally, but in LHTH, VO$_2$max was not
significantly greater than NT however, [Hb] was significantly greater in the NT. For LLTH, VO2max was significantly greater than NT, however [Hb] and Hct were not greater than NT. Since [Hb] and Hct were not greater than zero, this suggest other factors besides [Hb] and Hct to effect VO2max and improve SL performance in LLTH. Further, our results indicate the ES_Corr from HM for VO2max has a positive and significant correlation with ES_Corr for performance. However, there seems to be no relationship between VO2max and [Hb]/Hct. It is therefore fair to assume other adaptations may have occurred causing the observed increase in performance. These are similar conclusion drawn by Gore, Clark, and Saunders (2007), and Hendriksen and Meeuwsen (2003).

It has been proposed by Wilber, Stray-Gundersen, and Levine (2007) that LHTL results in stabilization of hypoxic inducible factor 1α (HIF-1α). Stabilization of this protein induces molecular adaptations causing increase in red cell mass and VO2max (Wilber, Stray-Gundersen, and Levine, 2007). However, this proposed adaptation to living in a hypoxic environment while training near SL may not be the mechanism. If this mechanism were so, the largest ES_WM from this current analysis would be from LHTL not LHTH or LLTH. In both LHTH and LLTH, exercise training was conducted in an hypoxic environment. This suggests a synergistic effect of endurance training and hypoxic exposure as a possible stimulus for physiological adaptations. In a review, Coffey and Hawley (2007) reported that molecular adaptations to endurance training are increases in peroxisome proliferator activated receptor γ co-activator 1α (PGC-1α), a protein that has been determined to promote mitochondrial biogenesis (Liang & Ward, 2006). The main regulator of PGC-1α has been reported to be adenosine monophosphate
– activated protein kinase (AMPK) (Coffey & Hawley, 2007). In a hypoxic environment, the hypoxia seems to activate AMPK in pulmonary arterial smooth muscle (Evans, 2006). In skeletal muscles utilizing rat models, activation of AMPK has been shown to increase PGC-1α (Ircher et al. 2003).

A possible explanation is that hypoxia is a metabolic stressor that increases the AMP/ATP ratio thereby signaling increases in AMPK (Evans, 2006). But when investigating activation of AMPK in eight healthy human male subjects on a cycle ergometer, at the same absolute training intensities (111 watts), there were no statistical differences in free AMP or activation of AMPK between the normoxic and hypoxic groups (Wadley et al. 2006). In contrast, using distance runners Zoll et al. (2006) reported that following six weeks of LLTH, the hypoxic group showed significant increases in oxidative enzymes as well as PGC-1α. Unfortunately, Zoll et al. (2006) did not measure AMPK activity, the regulator for PGC-1α in their investigation, which makes comparisons of results difficult. To our knowledge Wadley et al. (2006) has been the only group to investigate activity of AMPK in humans between a normoxic and hypoxic group. Therefore, more research maybe needed to investigate the relationship between AMPK and PGC-1α in a hypoxic environment.

Future Research

Unfortunately, analyses of AMPK, PGC-1α, and mitochondrial enzymes were not included in this current analysis, making it difficult to argue that these factors induce the adaptations that cause improvements in performance. Further research is needed to investigate the effects of these proteins in a hypoxic environment. Moreover, future
research may need to investigate the effects training in hypoxia may have on [Hb], Hct, and VO$_2$max. More specifically, in our results, both LHTH and LLTH groups improved performance, however, VO$_2$max, [Hb] and Hct response were different between the two groups. In addition, SL performance improvements are related to changes in VO$_2$max. Therefore, the need to investigate changes in VO$_2$max, [Hb], and Hct are needed.

Conclusion

Based on these results we conclude both LHTH and LLTH will provide the greatest benefits to improve SL exercise performance over NT in trained athletes. From our results, we suggest that enhancements in VO$_2$max may not be the sole mechanism for improvement in performance. Based on our results a relationship between VO$_2$max and performance exist, however, there seems to be no relationship between VO$_2$max and [Hb] or Hct. Consequently, because of the confounding results on VO$_2$max, [Hb], and Hct between LHTH and LLTH on SL performance, the mechanism has yet to be determined. More research is needed to investigate the effects of training in hypoxia so that the interaction between hypoxia and training on human physiology can be better understood.
REFERENCES


