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THE EFFECTS OF HIGH INTENSITY INTERMITTENT EXERCISE IN
NORMOBARIC HYPOXIA ON AEROBIC CAPACITY AND BODY
COMPOSITION IN OVERWEIGHT AND OBESE SEDENTARY ADULTS

By

Max W. Adolphs

THESIS

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SIGNATURE APPROVAL FORM

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ABSTRACT

By

Max W. Adolphs

Abstract The purpose of this study was to examine if high intensity intermittent exercise (HIIE) combined with normobaric hypoxia had a multiplicative effect on body composition, maximal oxygen uptake (VO_{2max}), and resting energy expenditure (REE) in overweight and obese sedentary adults. Twelve participants were recruited for the study. Participants were randomly assigned to either a hypoxic training (HT) group equivalent to 3,048 m ($F_{I}O_2 = 14.5\%$) or a normoxic training (NT) group equivalent to 0 m ($F_{I}O_2 = 20.9\%$) three times a week for six weeks in a normobaric hypoxic chamber. HIIE consisted of four .5 minute cycle ergometer sprints separated by 4.5 min light pedaling. Every two weeks another .5 minute sprint was added to a total of six by the final two weeks. Body composition was estimated by dual-energy x-ray absorptiometry (DXA scan), while VO_{2max} and REE were estimated via VO_2 assessment and indirect calorimetry. All variables were statistically analyzed pre and post training across and between groups using repeated measures ANOVA. Significant improvements were seen in REE ($P < .05$) and fat reductions ($P < .05$) across groups with no significant ($P > .05$) difference between groups, although mean values improved more in HT. A significant ($P < .05$) difference in VO_{2max} was seen between groups. Because HT showed significant improvement in VO_{2max} hypoxic HIIE might be a unique strategy for improving the aerobic capacity of overweight and obese sedentary adults.

Keywords High intensity intermittent exercise, Normobaric hypoxia, Maximal oxygen uptake, Dual-energy x-ray absorptiometry

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INTRODUCTION

Obesity is currently one of the biggest health threats facing the United States (U.S.) and other developed countries throughout the world. Using the U.S. as an example, sixty-nine percent of adults age 20 and older are overweight or obese, and approximately 300,000 deaths a year are obesity related (Finkelstein, 2009). While drug interventions and improved medical care may be slowing the mortality rate of individuals with obesity-related conditions, these are not long term solutions as obesity rates continue to rise (Flegal et al., 2012; Krumholz, 2014; Skinner et al., 2014). The economic burden from obesity is significant, costing the U.S. over 100 billion dollars a year. The average obese person accumulates 1,429 dollars more in medical costs per year when compared to a person of normal weight (Finkelstein, 2009). An effective long term solution to improving the health of Americans and reducing the prevalence of obesity remains elusive.

Even though the health benefits of aerobic exercise are well accepted there is a lack of participation and adherence to exercise (Bassett, 2008). This has led to the study of possible alternate, yet equally beneficial forms of exercise which are less time consuming than the traditional steady rate continuous exercise. From this research high-intensity intermittent exercise (HIIE) has arisen. This type of exercise consists of brief, intermittent bursts of vigorous activity, followed by periods of rest or low-intensity exercise (Gibala et al., 2012).

It has been demonstrated that the use of HIIE produces similar, if not greater improvements to VO_{2max} , body composition, and resting energy expenditure when compared to steady rate exercise (Burgomaster et al., 2008; Trapp et al., 2008). Aside from the positive effects of HIIE, it also has been shown to be more enjoyable than steady rate long duration exercise at the same total work, despite a higher rate of perceived exertion. (Bartlett, 2011). These findings suggest that

HIIE may be a time efficient and effective form of exercise that would be well tolerated and maintained by obese individuals assuming they are deemed healthy enough to participate in intense exercise .

High altitude or hypoxic training has been studied in sports and exercise science for decades as a potential aid to improving the performance of athletes through the hematological adaptations that occur at high altitude (Levine and Stray-Gundersen, 2005). It has not been until recently however, that hypoxic training has been studied as a potential aid for improving the health of overweight and obese individuals (Lippl et al., 2010; mackenzie et al., 2012; Netzer et al., 2008; Wiesner et al., 2010; Workman and Basset, 2012). Researchers have demonstrated that performing steady rate and interval exercise, or even simply sitting at high altitude for both prolonged and intermittent time periods, resulted in greater improvements to body composition, VO_{2max} , and resting energy expenditure than when performing the same exercise or sitting at sea level (Lippl et al., 2010; Mackenzie et al., 2012; Netzer et al., 2008; Wiesner et al., 2010; Workman and Basset, 2012).

No study to this date has examined what effects HIIE in hypoxic conditions may have on overweight and obese sedentary subjects. HIIE has been demonstrated to be an effective, time efficient, well perceived form of exercise, while hypoxic training has been demonstrated to be a potential aid to exercise for obese individuals. Therefore, the purpose of this study was to examine the effects of HIIE in normobaric hypoxia on aerobic capacity and body composition in obese sedentary adults. It was hypothesized that the synergistic effect of HIIE and hypoxia would result in greater improvements to body composition, resting energy expenditure (REE), and maximal oxygen uptake (VO_{2max}) when compared to a placebo group. If this was determined to be the case

than hypoxic HIIE may be a viable time-efficient and effective form of exercise which could be beneficial to overweight and obese sedentary adults.

Material and Methods

Participants

Twelve sedentary overweight and obese (per ACSM guidelines) adults volunteered for the study (Linda et al., 2014). Each participant was screened prior to being accepted into the study to establish that they were: (a) free of risk factors associated with cardiovascular, pulmonary or metabolic disease; (b) safe to participate in high intensity exercise; and (c) other than regular daily activities, not participating in any regular exercise (≤ 2 sessions per week and ≤ 30 min per session, for at least 1 year prior to the study). The study procedures and risks were explained to the participants, who provided written, informed consent. The participants were evenly and randomly assigned to either a hypoxic training (HT) group (males = 2, females = 4) or a normoxic training (NT) group (i.e., placebo) (males = 2, females = 4; age). Full descriptive data can be observed in Table 1. The experimental protocol was approved by the University Institutional Review Board.

Variables	HT group	NT group
Age (years)	48.8 \pm 7.1	54 \pm 8.0
Height (cm)	171.9 \pm 5.6	169.3 \pm 4.8
Body Fat %	38.9 \pm 7.9	39.4 \pm 6.4

Table 1. Average descriptive data and standard deviation of subjects

Procedures

The hypoxic training group (HT) exercised in a normobaric hypoxic chamber (Hypoxico Inc., New York, NY) which simulated an altitude of 3,048 m ($F_{I}O_2 = 14.5\%$). The normoxic

training group (NT) exercised in the same chamber as HT but at different times. NT was told the chamber was set at 3,048 m or “low oxygen” but were unknowingly exercising at sea level or normoxic conditions ($F_{I}O_2 = 20.9\%$). Both groups followed the same schedule of three training days per week, with at least one day in between for six weeks (18 total sessions). Each session consisted of repeated 0.5 minute intervals of all-out effort on a cycle ergometer against a resistance equivalent to approximately $0.05 \text{ kg} \cdot \text{kg}^{-1}$. Recovery between work intervals was fixed at 4.5 min, during which time participants cycled ($< 50 \text{ rpm}$) at a power requirement of approximately 30 Watts. The number of intervals performed during each training session increased from four during weeks 1 and 2, to five during weeks 3 and 4, and six by weeks 5 and 6.

All subjects underwent testing pre- and post-training to determine REE. In order to achieve the most accurate result, prior to REE assessment, participants were asked to: (a) engage in no exercise for 36-hours; (b) ingest no caffeine or alcohol for 24-hours; (c) eat their last meal before 20:00 the night before and drink only water afterwards; (d) travel to the laboratory by car or public transportation; (e) and rest for 10-minutes on a bed in a quiet environment immediately before metabolic data collection. Upon arrival to the laboratory, participants were placed in a comfortable, supine position in a quiet environment in preparation for metabolic rate measurement via indirect calorimetry technique (CareFusion version Vmax29, San Diego, CA). The participants were instructed to remain quiet and relaxed during data collection without falling asleep. Once the data was collected, the modified Weir equation was used to determine REE (Weir, 1949).

All subjects underwent a dual-energy X-ray absorptiometry (DXA) scan (Lunar Prodigy; GE Healthcare, Madison, WI) for body composition determination pre- and post-study. Subjects were instructed to follow the same protocol prescribed for resting metabolic rate testing and to stay hydrated. They were also asked to wear minimal clothing, and all jewelry and metal objects were

removed before the scan. Body composition was measured from a whole body scan using a narrow fan beam DXA with analysis performed using GE Encore software (GE Healthcare). The DXA was calibrated with phantoms as instructed by the manufacturer's guidelines before testing.

Subjects performed an exercise test until exhaustion for determination of VO_{2max} pre- and post-study. A ramp protocol was utilized (increasing 1 W every 2 s) on an electronically braked cycle ergometer (Lode BV, Excalibur Sport, the Netherlands) until fatigue (Burgomaster et al., 2008). In order to determine peak oxygen uptake, expired air analysis was utilized. VO_{2max} was determined as the highest 30 second average during the test (Burgomaster et al., 2008)

Statistical Analysis

All statistics analyses were conducted using SPSS for Windows software (SPSS Inc., Chicago, IL). Independent t-tests for independent samples were used to compare baseline characteristics of both training groups. A two way repeated measures mixed ANOVA [with main effects of time (pre- vs. post-training)] was used to examine changes in each group (i.e., HT group vs. NT groups) as well as between groups. All data are presented as mean and standard deviation with p values of less than 0.05 assumed to indicate statistical significance.

Results

Resting Energy Expenditure.

REE significantly increased in both groups following training ($F = 7.5$, $P = .021$) with no significant difference between groups ($F = .159$, $P = .698$; see Fig. 2). HT and NT increased energy expenditure 13.04% and 11.76%, respectively (Table 2).

Body Composition.

Body fat was significantly decreased in both groups following the training ($F = 6.105$, $P = .033$) with no significant difference between groups ($F = .065$, $P = .803$; see Fig. 3). HT and NT decreased body fat 3.07% and 2.00%, respectively (Table 2).

VO_{2max}

Significant increases in VO_{2max} was observed in both groups following the study ($F = 39.255$, $P < .001$). A significant difference was also observed between groups ($F = 9.565$, $P = .011$), which indicated HT increased VO_{2max} to a greater degree than NT. HT and NT increased VO_{2max} 33.8% and 10.9%, respectively (Table 2, Figure 1).

	HT		NT	
	Pre	Post	Pre	Post
REE kcal·min ⁻¹	1.15 ± 0.34	1.30 ± 0.30*	1.02 ± 0.20	1.14 ± 0.16*
Weight kg	32.27 ± 9.98	31.28 ± 10.75*	33.56 ± 9.53	32.89 ± 9.06*
VO ₂ ml·kg ⁻¹ ·min ⁻¹	22.93 ± 6.9	30.7 ± 6.2*	24.27 ± 7.64*	26.92 ± 7.07*

Table 1. Variables from pre to post HIIE in HT and NT. * significantly different from pre training.

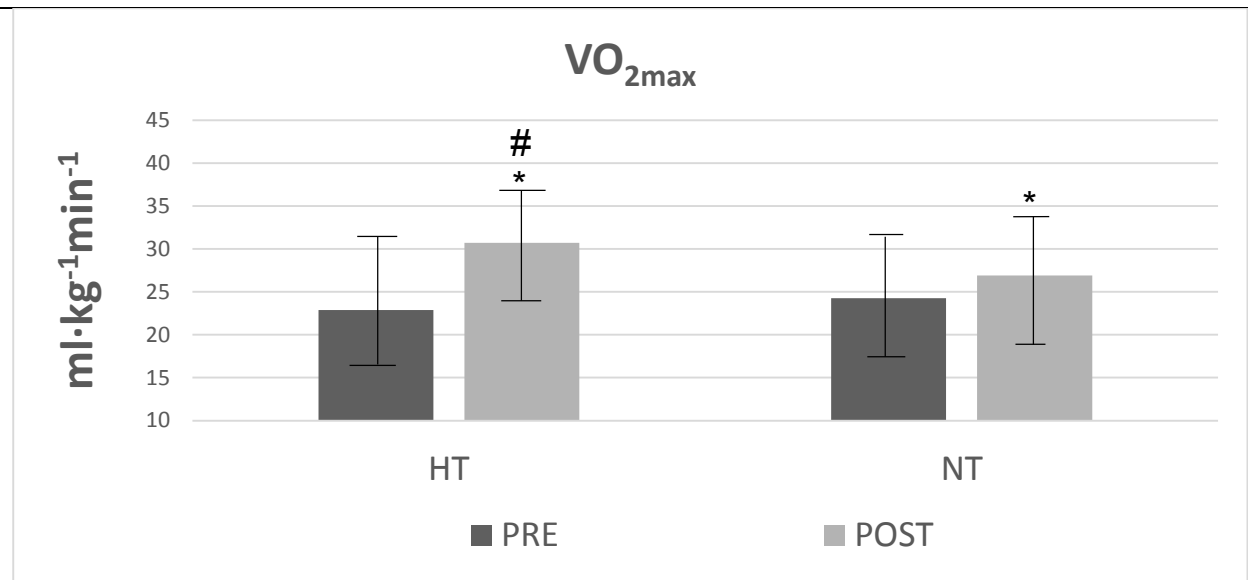


Figure 1 – Improvement in VO_{2max} pre and post training in HT and NT. * Significant difference pre- to post-training. # significant difference vs. NT.

Discussion

The purpose of this study was to examine the effects of HIIE in normobaric hypoxic conditions on aerobic capacity and body composition in overweight and obese sedentary adults. To the authors' knowledge, this was the first study protocol to examine an overweight and obese sedentary adult population in hypoxia undergoing HIIE. As hypothesized there were greater improvements to VO_{2max} in HT versus NT. While not statistically significant, HT did increase resting energy expenditure and improved body composition more than NT. The main outcomes of this study confirmed prior research reporting HIIE and hypoxic exposure as a means to improve aerobic capacity.

VO_{2max}

In the present study both HT and NT significantly improved VO_{2max} . These results support previous studies illustrating HIIE to significantly increase VO_{2max} despite a small time commitment (Burgomaster et al., 2008; Gibala et al., 2012). These researchers suggest that the

significantly increased VO_{2max} was likely induced by increases in mitochondrial capacity from HIIE (Gibala et al., 2012). Peroxisome-proliferator activated receptor γ coactivator (PGC)-1 α , is regarded as the master regulator of mitochondrial biogenesis in muscle, and recent researchers have shown (PGC)-1 α to increase significantly hours after acute bouts of HIIE (Gibala et al., 2012; Gibala et al., 2009; Little et al., 2011). The significant increases in (PGC)-1 α is believed to be initiated by the intensity of exercise, not the duration. The mechanism behind this starts with the changes in ATP to AMP ratio after exercise. High levels of AMP during exercise leads to increased phosphorylation and decreased dephosphorylation of AMPK (Corton et al., 1995). Increased concentrations of AMPK have been shown to activate (PGC)-1 α in skeletal muscle, ultimately leading to increased mitochondrial biogenesis (Gibala et al., 2012; Gibala et al., 2009; Little et al., 2011).

While both groups significantly improved VO_{2max} , HT improved to a significantly greater degree than NT. These results agree with our initial hypothesis and support the previous studies that have shown exercise in hypoxia to increase VO_{2max} to a greater degree than normoxic exercise (Czuba et al., 2013; Zoll et al., 2006). It has been suggested that hypoxic exposure increases VO_{2max} through improvements in O_2 transport by stimulating erythropoietin which results in increased reticulocyte count, hemoglobin, and hematocrit levels (Wilber et al., 2001). While it is possible these variables were associated with the increase in VO_{2max} seen in HT, most studies suggest these improvements are only realized with greater lengths of exposure (Levine and Stray-Gundersen, 2005; Wilber et al., 2001). Researchers have also shown that high intensity hypoxic exercise protocols lead to significant increases in (PGC)-1 α and monocarboxylate transporter 1 (MCT1) post training (Czuba et al., 2013; Zoll et al., 2006). With increases in (PGC)-1 α and MCT1,

individuals have may have an increased mitochondrial capacity and ability to buffer lactate. These two factors are more likely contributors to the increased VO_{2max} observed in HT versus NT.

Resting Energy Expenditure

Both HT and NT significantly increased REE pre- to post-study. These results agree with previous research which has shown exercise programs to significantly increase REE post intervention in obese individuals (Kelly et al., 2013; Skelly et al., 2014). While there was no significant difference between groups, HT increased REE (13.04%) to a greater degree vs. NT (11.06%). Due to these results, it is feasible that if the study had been carried out for a longer period of time and there had been more participants, HT may have increased REE significant more than NT.

Body Composition

Both HT and NT significantly decreased body fat pre- to post-study. These results are in line with the previous researcher that has reported HIIE to significantly augment fat loss (Trapp et al., 2008). researchers have reported significant excess post-exercise oxygen consumption (EPOC) and consequently significantly elevated REE immediately post HIIE which may contribute to the fat loss from HIIE (Kelly et al., 2013; Skelly et al., 2014). It is also possible that suppression of appetite from HIIE contributes to the fat loss seen (Sim et al., 2014)

While there was no significant difference between groups, all participants in HT (3.07%) lost more fat than participants in NT (2.00%). From these results it can be postulated that if there had been a greater number of participants and the study had been carried out for a longer period of time, HT may have shown significantly greater fat loss compared to NT. Hypoxic exposure has been reported to decrease appetite by potentially increasing the satiety hormone leptin and decreasing the hunger hormone ghrelin (Chaiban et al., 2008). While both these effects possibly

contributed to increased fat loss in HT with the current study, it is more likely, due to the periods of exposure being very brief, that the major contributors to the fat loss in HT were increased REE for reason discussed earlier and increased EPOC. The anaerobic stimulus created by hypoxia coupled with HIIE likely exacerbates EPOC.

Conclusion

The results related to this study suggest that hypoxic HIIE may be a unique strategy for augmenting VO_{2peak} , in overweight and obese sedentary adults. Hypoxic HIIE is also non-pharmacological and time efficient. These added benefits have the potential to limit side effects from commonly utilized obesity drugs as well as potentially increase exercise retention rates among obese individuals. Ultimately, if overweight and or obese sedentary adults are deemed healthy enough to participate in an exercise program, hypoxic HIIE could be considered for an alternate strategy to improve their health and aerobic capacity.

II. LITERATURE REVIEW

Introduction

Continuous steady rate exercise has long been recognized as an effective means to improve functional capacity and prevent and attenuate obesity and its associated metabolic abnormalities. High-intensity intermittent exercise (HIIE) has recently been demonstrated to be a more time efficient and yet potentially equally beneficial form of exercise when compared to traditional steady rate exercise (Gibala, 2012). Intermittent normobaric hypoxia or simulated altitude has also been shown in the recent literature to be an effective aid in reducing adiposity and improving functional capacity in obese and sedentary individuals (Workman and Basset, 2012; Lippl et al., 2010). Therefore, it seems reasonable to assume HIIE combined with normobaric hypoxia will have a multiplicative effect on functional capacity and body composition.

This literature review will document and critically evaluate peer reviewed literature which support, or provide contextual information for, the determination of whether High-intensity intermittent exercise in normobaric hypoxia will have a multiplicative effect on functional capacity, body composition, and metabolic health in overweight and obese sedentary adults. The review is divided into three sections. The first section describes the pathophysiology of obesity, the second section examines the effects of high-intensity intermittent exercise on overweight and obese sedentary adults, and the third section elucidates the physiological responses of hypoxic exposure both sitting and exercising in overweight and obese sedentary adults. This review forms a foundation for the hypothesis of the current study.

Pathophysiology of Obesity

Just like most species, humans are constantly driven to eat to survive. Through the development of technology humans are no longer like other species in the fact that they no longer have any real need to be physically active as a natural part of the life, and have a complete overabundance of cheap non-nutrient dense, high caloric foods. These two factors do not bode well together when considering the development of obesity (Basset, 2008). As humans have become more obese they have become more unhealthy (Ahima and Flier, 2000).

It is now recognized that obesity, particularly visceral obesity, which is defined as having an accumulation of large adipocytes in and around the stomach, contributes to and causes many different metabolic abnormalities (Tchernof and Després, 2013). The three most recognized metabolic issues that are linked to obesity which will be discussed are hypertension, dyslipidemia, and type two diabetes.

Hypertension

Hypertension or high blood pressure has been linked to obesity in many studies (Black, 2003). Hypertension occurs when blood vessels have an increased resistance to blood flow (Black, 2003). Elevated blood pressure naturally occurs during times of arousal to move larger quantities of blood to desired organs, however, during a resting state, blood pressure should not be elevated as seen in a large majority of the obese population (Bassett, 2008).

As a lone issue hypertension in most cases is not fatal, however the many cardiovascular complications which have been shown to arise from hypertension such as left ventricular hypertrophy, atrial and ventricular arrhythmias, diastolic heart failure, systolic heart failure, and

most commonly ischemic heart disease with or without congestive heart failure have been. (Black 2003).

One possible mechanisms underlying the development of hypertension in obese individuals is altered angiotension II and aldosterone secretion (Zorad, 1995). Obesity has also been shown to cause structural changes to the kidneys which interfere with and eventually cause the total loss of nephron function resulting in hypertension (Hall 2003). Ectopic fat deposits on the kidneys measured by CT have also been shown to be predictive of hypertension (Tchernof and Després, 2013).

Atherosclerosis

Atherosclerosis or ischemic heart disease arises from the dyslipidemic state frequently observed in obese individuals (Tchernof and Després, 2013). Atherosclerosis occurs when an artery wall thickens due to the invasion of triglycerides, cholesterol, and white blood cells (Lang et al. 2011). The development of atherosclerosis can be influenced by a variety of factors such as obesity, genetics, dietary choices, and the environment (Lang et al. 2011). While there are many possibilities and theories for how these factors initiate atherosclerotic development, most scientific literature points towards being overweight and or obese, as one of the primary driving factors (Tchernof and Després, 2013).

Visceral fat has been shown to easily allow monocyte infiltration (Tchernof and Després, 2013). Once within the visceral fat the monocytes differentiate into macrophages which release a variety of cytokines such as IL-6 and TNF- α (Trayhurn and Wood, 2005). These cytokines, aside from driving hypertension as discussed previously and diabetes which will be discussed later, also influence the visceral adipocytes which are very hyperlipolytic, meaning they easily releases fatty acids into the blood stream (Trayhurn and Wood, 2005). The excess fatty acids in the blood

stream released from visceral fat are packaged into very low density lipoproteins (VLDL) in the liver and released back into the blood stream resulting in hypertriglyceridemia, a risk factor for atherosclerosis. The excess VLDL or hypertriglyceridemia is associated with atherosclerosis in part because of its ability to decrease levels of high density lipoproteins (HDL) cholesterol and increase pattern B low density lipoprotein (LDL) cholesterol (Tchernof and Després, 2013).

Increased VLDL's influence on decreased HDL cholesterol and increased pattern B LDL cholesterol is through VLDL exchanging its triglycerides for LDL's and HDL's cholesterol esters, thus making LDL and HDL substrates for hepatic triglyceride lipase (HTL). HTL removes LDL and HDL's triglycerides, subsequently making them small and dense (Pascot et al., 2001). These small dense HDL are easily cleared from the blood resulting in decreased levels of circulating HDL, while the small dense LDL are able to penetrate the endothelium of the arterial wall (Pascot et al., 2001). Once within the endothelium or tunica intima the LDL remain there due to the decreased levels of HDL which typically would assist in removing it. Over time the LDL are oxidized by enzymes and free radicals which results in an inflammatory response (Tchernof and Després, 2013).

From the inflammatory response, monocytes enter into the endothelium and differentiate into macrophages which phagocytize the oxidized LDL forming foam cells termed "fatty streaks". The foam cells die over time which results in a greater inflammatory response coupled by the continued infiltration of LDL and consequent oxidation of cholesterol (Pascot et al., 2001). The foam cells and damaged endothelial cells cause proliferation of smooth muscle cells from the tunica media into the endothelium which form a fibrous capsule around the fatty streak which as a whole is termed an atheroma (Austin, 1988).

Over time continued development of atheroma's leads to stenosis or narrowing of the lumen (Austin, 1988). The normally thin tunica intima becomes the thickest layer of the vessel with large lighter colored atheroma's within. This narrowing leads to increased pressure within the arteries and eventual ruptures of atheroma's. A rupture of an atheroma causes blood clotting and obstruction of blood flow which typically results in a myocardial infarction or heart attack (Austin, 1988). If the heart attack is not fatal the rupture is then covered by a fibrous organization which results in greater stenosis. The increased stenosis further increases pressure within the arteries which increases the chance of another atheroma rupture and consequent heart attack (Pascot et al., 2001).

Type Two Diabetes

Lots of evidence exists for the association between obesity and insulin resistance which ultimately results in type two diabetes (Karter, 2005). Insulin resistance occurs when insulin can no longer bind to its tyrosine kinase receptor, consequently resulting in a lack of glucose transporter 4 (GLUT4) translocation to the cell membrane which is what normally allows glucose into the cell (Karter, 2005). This results in abnormally high levels of not only glucose, but insulin, which over time can lead to kidney failure, acidosis, and death if not treated (Karter, 2005).

The metabolic profile of visceral fat is one possible mechanism of how obesity influences insulin resistance. As discussed earlier, the hyperlipolytic visceral adipocytes easily release fatty acids into circulation through the influence of inflammatory cytokines (Tchernof and Després, 2013). The overexposure of non-esterified fatty acids impairs liver metabolism leading to the overproduction of apolipoprotein B-containing lipoproteins, increased hepatic glucose production, and reduced hepatic degradation of insulin, which exacerbates systemic hyperinsulinemia (Tchernof and Després, 2013).

Another possible mechanism by which obesity influences insulin resistance is through production of cytokines such as TNF- α and IL-6 which result in a systemic inflammatory state, disrupting insulin receptor function. It has also been proposed that visceral obesity may prevent subcutaneous fat from expanding and acting as a buffer to protect other organs such as the pancreas from ectopic fat deposits (Tchernof and Després, 2013).

High-intensity Intermittent Exercise and Obesity

While the benefits of exercise are well accepted there is a lack of participation and adherence to exercise (Bassett, 2008). This has led to the study of possible alternate, yet equally beneficial forms of exercise which are less time consuming than the traditional steady rate continuous exercise. Recent research examining HIIE, looks promising in terms of significantly improving aerobic capacity, reducing adiposity, and improving metabolic risk factors in a time efficient manner (Sim et al., 2014; Whyte et al., 2010; Trapp et al., 2008).

Aerobic Capacity

There have been multiple studies that have shown HIIE to improve VO_{2max} to an equal or greater degree than steady rate exercise when given the same workload (Burgomaster, 2008; Gibala, 2012). For example, Burgomaster et al. (2008) examined the effects of HIIE versus steady state exercise (SSE) in 20 untrained but otherwise healthy 23 year olds over the course of six weeks. Participants were split evenly between the HIIE and SSE group. HIIE consisted of 30 seconds all out sprint Wingate tests followed by 4.5 minutes of recovery three times per week. SSE consisted of 40-60 min of 65% VO_{2max} three times per week. Despite the HIIE group doing significantly less work compared to the SSE group (225 vs. 2250 KJ per week), there was no difference in improvements to VO_{2max} pre to post study.

Burgomaster et al. (2008) examined some physiological variables and determined that the significant increases in VO_{2max} seen from HIIE, despite less time commitment and total work are likely induced by increases in mitochondrial capacity. Peroxisome-proliferator activated receptor γ coactivator (PGC)-1 α , is regarded as the master regulator of mitochondrial biogenesis in muscle, and this study found (PGC)-1 α , as well as citrate synthase, another strong indicator of mitochondrial biogenesis, to increase similarly after HIIE and SSE suggesting that intensity and not duration is the primary driving factor (Figure1).

The mechanism underlying the significant increases in (PGC)-1 α seen from HIIE is likely initiated by changes in the ATP to AMP ratio after exercise. High levels of AMP during exercise leads to increased phosphorylation and decreased dephosphorylation of AMPK which promotes the nuclear translocation of (PGC)-1 α and consequent increase in mRNA of many mitochondrial genes (Corton et al., 1995). Increases in the Activation of p38 mitogen-activated protein kinase driven by increased generation of reactive oxygen species may also be involved (Gibala et al., 2012; Gibala et al., 2009; Little et al., 2011).

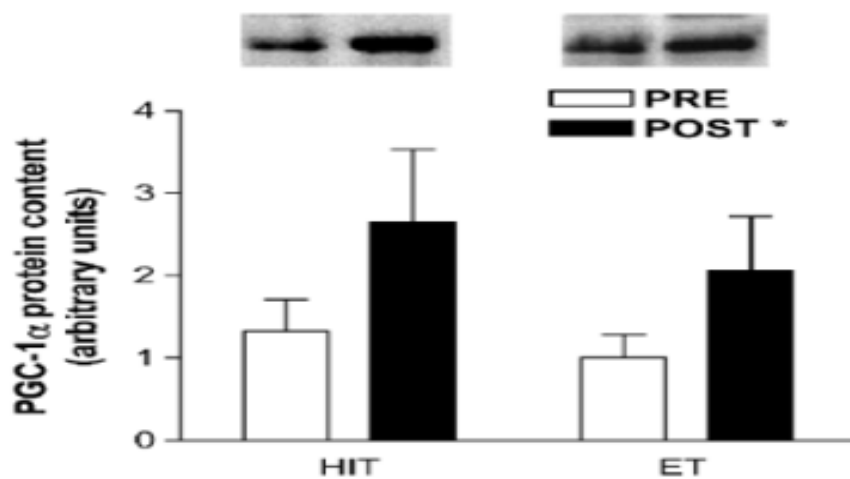


Figure 1. (PGC)-1 α pre to post HIIE and steady rate exercise (Burgomaster et al., 2008)

Hypertension

Numerous studies have shown HIIE to have beneficial effects on blood pressure (Gillen et al., 2014; Whyte et al., 2010). Gillen et al. (2014) examined the effects of HIIE on 14 Overweight and or obese but otherwise healthy men and women. HIIE consisted of 18 sessions of three, 20 second “all-out” sprints against 5.0% body mass (mean power output: ~450–500 W) interspersed with two min of recovery at 50 Watts. Post training resting mean arterial pressure decreased by 7% as portrayed in figure 2.

Resting SBP (mmHg)	124 \pm 8	116 \pm 8*	109 \pm 11	100 \pm 11*
Resting DBP (mmHg)	71 \pm 11	67 \pm 5	66 \pm 9	60 \pm 9
Resting MAP (mmHg)	88 \pm 8	83 \pm 4*	80 \pm 10	74 \pm 9*
Relative PPO (W/kg FFM)	11.3 \pm 4.1	12.2 \pm 3.6*	10.0 \pm 0.6	11.8 \pm 1.1*
Relative MPO (W/kg FFM)	9.0 \pm 1.6	10.6 \pm 1.5*	9.0 \pm 0.5	12.0 \pm 0.1*

Values are means \pm S.D. N=7 for men and women. *Significantly different than pre-training ($p\leq 0.05$).
FPG, fasting plasma glucose; FPI, fasting plasma insulin; Gmax: daily peak glucose concentration.
doi:10.1371/journal.pone.0111489.t002

Figure 2. Resting mean arterial pressure pre and post HIIE (Gillen et al., 2014).

Type Two Diabetes

Studies have demonstrated beneficial changes in insulin sensitivity after just a few sessions of HIIE (Whyte et al., 2010; Little et al., 2010). For example, Little et al. (2010) demonstrated that just six sessions of HIIE over two weeks reduced average 24 hour blood glucose concentration and postprandial glucose excursions. The acute improvements in insulin sensitivity is likely a result of increased skeletal muscle GLUT4 content after HIIE allowing greater amounts of glucose into the cell, consequently lowering extra cellular glucose levels (Figure 3) (Little 2011).

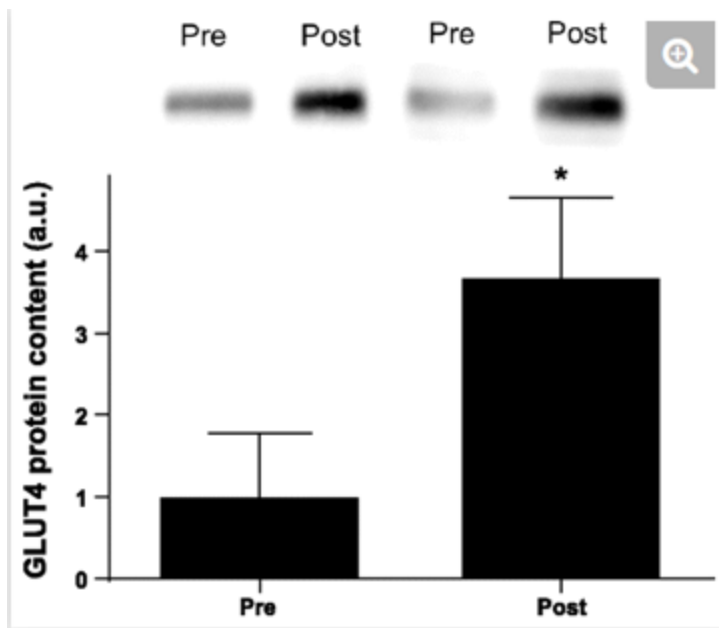


Figure 3. GLUT4 pre and post HIIE Training (Whyte et al., 2010)

Weight Loss

While the short term effects of HIIE have proven to be beneficial, there is a lack of studies looking at the long term effects. Of the HIIE studies done lasting longer than six weeks, the results have proven promising (Trapp et al., 2008; Tremblay et al., 1994). In one such study, Trapp et al. (2008) looked at the effects of HIIE versus steady rate exercise three times a week over the course of 15 weeks in 45 inactive, but otherwise healthy women. The participants were split evenly into either a HIIE or SSE group. In this study the HIIE protocol consisted of 8 seconds of springing against .5kg followed by 12 seconds of recovery lasting between 5 and 20 minutes. The SSE group pedaled at rate equivalent to 60% VO_{2max} between 20 and 40 minutes. Despite less time commitment, HIIE produced significantly greater fat reductions than steady

rate. exercise despite the reduced time commitment (Figure 4).

<i>Group</i>	<i>Leg fat (kg)</i>	<i>Leg lean (kg)</i>	<i>Leg, % fat</i>	<i>Trunk fat (kg)</i>	<i>Trunk lean (kg)</i>	<i>Trunk, % fat</i>
HIIE pretraining	8.0±1.2	13.1±0.5	36.6±3.0	11.4±2.0	18.3±0.8	36.5±3.4
HIIE post training	6.8±0.8	13.2±0.5	33.2±2.2 ^a	10.0±1.6 ^b	18.8±0.8 ^b	33.2±2.9 ^{a,b}
SSE pretraining	7.3±0.7	13.2±0.6	35.4±2.4	8.6±1.3	18.6±0.8	30.9±3.7
SSE post training	7.0±0.5	13.1±0.6	34.8±2.0	8.8±1.2	18.3±0.8	31.8±3.6
CONT pretraining	8.9±1.2	13.3±0.5	38.1±2.4	11.0±1.5	18.3±0.6	35.3±2.9
CONT post training	8.7±1.1	13.2±0.5	38.1±2.1	11.0±1.3	18.0±0.5	36.1±2.6

Abbreviations: CONT, control; HIIE, high-intensity intermittent exercise; SSE, steady-state exercise.

^aHIIE significantly different from CONT, $P < 0.05$.

^bHIIE significantly different from SSE, $P < 0.05$.

Figure 4. Fat percentage pre to post HIIE and steady rate exercise (Trapp et al., 2008)

The possible mechanisms underlying the fat loss effects from HIIE may be increased fat oxidation and decreased appetite after exercise (Sim et al., 2013). As mentioned earlier, recent studies have shown HIIE to significantly increase the oxidative capacity of muscle, likely driven by increases in mitochondrial capacity (Burgomaster, 2008; Gibala, 2012). Sim et al. (2013) has also demonstrated that HIIE decreases post-exercise ad-libitum energy intake to a greater degree when compared to steady rate exercise. This greater decrease in appetite following HIIE is likely influenced by changes in hunger hormones such as leptin, ghrelin, and peptide YY, but more definitive research is needed to garner a better understanding (Sim et al., 2013).

As discussed earlier, both insulin resistance and dyslipidemia have been linked to the actual accumulation of visceral adipocytes (Tchernof and Després, 2013). Thus, a reduction in body fat has proven to be very beneficial in the metabolic health of obese individuals by reducing the amount of monocyte infiltration and consequent cytokine production which causes

the systemic inflammation commonly seen in obese individuals (Van Pelt et al., 2014). This reduction in body fat and subsequent reduction in cytokine production also results in a decrease of non-esterified fatty acids to the liver, which is another known cause of metabolic disease (Van Pelt et al., 2014).

Aside from the positive long and short term effects of HIIE, it also has been shown to be more enjoyable than steady rate exercise at a given workload despite a higher rate of perceived exertion (Bartlett et al., 2011). These findings suggest that HIIE may be a time efficient and effective form of exercise that would be well tolerated and maintained by obese individuals, assuming they are deemed healthy enough to participate in intense exercise .

Hypoxia and Obesity

High altitude or hypoxic training has been intensely studied as an aid to improving the performance of athletes through the physiological adaptations which occur at high altitude (Levine and Stray-Gundersen 2005). Recent research however, while limited, has shown the potential for intermittent hypoxic exposure, both sitting and exercising, as a tool for improving the functional capacity, body composition, and ultimately overall health of overweight and obese individuals (Lippl et al. 2010; mackenzie et al. 2012; Netzer et al. 2008; Wiesner et al. 2010; Workman and Basset 2012).

Aerobic Capacity

The majority of studies overtime which have demonstrated improvements in functional capacity from hypoxic exposure have been in predominantly athletes and used the “live high train low” principal. The “live high train low” principal is where individuals or athletes benefit from hypoxic exposure by living at altitude and training at sea level. This has been shown to work by the adaptations that occur when ones lives at altitude. To compensate for lowered partial

pressure of oxygen the human body improves O₂ transport by stimulating erythropoietin which results in increased reticulocyte count, hemoglobin, and hematocrit levels (Wilber et al. 2001). Due to the increased red blood cell mass, when the individual trains at sea level they are able to transport more oxygen and utilize for oxygen which results in performance enhancement. While the “live high train low” principal may feasibly be beneficial for overweight and obese sedentary adults, it is not practical to live at altitude or in a hypoxic chamber which has led to studies examining the effects of intermittent exposure.

Most studies which have examined the effects of intermittent hypoxic exposure on functional capacity compared to the same exercise at sea level have shown little to no improvements until recently. The reason for these previous studies showing little to no improvements is likely due to the fact that they utilized a study design which consisted of continuous steady rate exercise. The more recent studies which have shown greater improvement to functional capacity when compared to the same exercise have used higher intensity anaerobic exercise. The reason for this type of exercise producing these results is still yet to be fully understood but likely is associated with improvements to mitochondrial capacity. This has been demonstrated by Zoll et al. (2006) who showed that high intensity intermittent hypoxic exercise resulted in significantly higher concentrations of PGC-1 α when compared to the same exercise at sea level. The hypoxic conditions coupled with anaerobic exercise likely has a multiplicative effect driving the greater concentrations of PGC-1 α .

Health Implications

Researchers have demonstrated that doing steady rate exercise, or even simply sitting at high altitude for both prolonged and intermittent time periods, results in greater improvements to body composition and metabolism than when performing the same exercise or sitting at sea level

(Lippl et al. 2010; mackenzie et al. 2012; Netzer et al. 2008; Wiesner et al. 2010; Workman and Basset 2012). Lippl et al. (2012) demonstrated that a week stay at an altitude of 2760m resulted in significantly greater weight loss when compared to a control group. Studies examining exercise at altitude have also shown body fat reductions. Wiesner et al. (2010) and Netzer et al. (2008) both demonstrated that steady rate exercise of 60-65% VO₂max at altitude over 4 and 8 weeks respectively resulted in greater fat reductions than the same exercise at sea level.

The mechanisms underlying the fat loss effects of hypoxia are likely associated with increased energy expenditure, muscle oxidative capacity, and appetite suppression. In a study by Workman and Basset (2012) it was shown that overweight individuals increase their resting energy expenditure by simply sitting at a simulated altitude of 3,048m for three hours. As discussed earlier, anaerobic exercise in hypoxic conditions has also been shown to increase mitochondrial capacity (Zoll et al., 2006). Lastly, Hypoxic exercise has been shown to effect hunger hormone concentrations. Lippl et al. (2012) found that hypoxic exercise resulted in significant increases in leptin and decreases in ghrelin. These alterations in hunger hormones suggest that altitude stimulates weight loss not just through increases in energy expenditure and oxidative capacity, but possibly by suppressing appetite.

III. CONCLUSIONS AND RECOMMENDATIONS

Conclusions

If the results related to this study are confirmed, than hypoxic HIIE may be a new and unique strategy for augmenting VO_{2peak} , lean leg mass, body fat reductions, and REE in obese individuals. Aside from the positive metabolic effects, hypoxic HIIE is non-pharmacological and time efficient. These added benefits have the potential to limit side effects from commonly utilized obesity drugs as well as potentially increase exercise retention rate among obese individuals. Ultimately, if obese adults are deemed healthy enough to participate in an exercise program, hypoxic HIIE could be considered for an alternate strategy to improve their health and functional capacity.

Recommendations

Future research should focus on the mechanisms by which high intensity exercise in hypoxia augments aerobic capacity. While there are a few studies looking at high intensity exercise in hypoxia on athletic populations, there are currently no studies looking exclusively at overweight and obese populations. Future studies should determine if PGC-1 α is increased in the same manner seen in athletic populations. Mitochondrial density should also be studied along with PGC-1 α to see if there is a direct relationship.

More extensive research also needs to be done to determine how hypoxia induces fat reductions. While a few studies have shown hypoxia to augment oxidative capacity, there are currently very few studies which have looked at the variable of hunger. The few studies which do exist on the matter suggest hypoxia may influence ghrelin and leptin inversely resulting in suppressed appetite. Future research should use ad-libitum eating post-hypoxic exposure along

with blood samples to determine if alterations in ghrelin and leptin are associated with changes in actual eating habits.

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APPENDICES

APPENDIX A

Title of Project: The Metabolic Effects of High Intensity Intermittent Exercise in Hypoxia versus Normoxia on Sedentary Overweight Adults

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1. **Purpose of the Study:** The purpose of this research study is to determine the metabolic effects of exercise in hypoxia on sedentary overweight but otherwise healthy adults.
2. **Procedures to be followed:** You will be asked to report to the exercise science laboratory at Northern Michigan University to exercise in a hypoxic chamber set at 14% oxygen concentration equal to 10,000 feet. The exercise will consist of .5 minutes sprints followed by 4.5 minutes of recovery totaling 20 minutes for week one and two, 25 minutes for week three and four, and 30 minutes for week five and six. You will also receive baseline and retesting of metabolic responses at the beginning middle and end of the study. These tests will consist of a DEXA scan, which is an X-ray machine that will pass over you as you lay supine for determining body fat percentages and metabolic testing which will consist of resting in the supine position for 30 minutes while connected to the VMax (viasys) for determination of resting metabolic rate and substrate utilization. You will also do an exercise test on the cycle ergometer (Excalibur Sport Bike) while connected to the VMax (viasys) for determination of VO_2 max and peak power output.
3. **Discomforts and Risks:** While uncommon in healthy individuals, exercise can cause discomforts and risks such as fatigue, nausea, dizziness, lightheadedness, shortness of breath, muscle soreness, injuries such as pulled and torn muscles, heart arrhythmias, heart attacks, and death. Exercising in hypoxia can potentially exacerbate these risks. You will be monitored at all times to ensure minimal risk by an individual certified in AED and first aid. AED, first aid, and supplemental oxygen will also be available on site.

4. **Benefits:** You will have the opportunity to potentially to lose weight, reduce risk factors, and in general become healthier in a time efficient, non-invasive, non-surgical, and non-pharmacological way.
5. **Duration:** The study will consist of exercising three days per week for six weeks.
6. **Statement of Confidentiality:** Your participation in this research is confidential. The data will be stored and secured at Northern Michigan University in a password protected file. Northern Michigan Universities Institutional Review Board may review records related to this research study. In the event of a publication or presentation resulting from the research, no personally identifiable information will be shared.
7. **Right to Ask Questions:** Please contact Dr. Brian Cherry of the Human Subjects Research Review Committee of Northern Michigan University (906-227-2300) bcherry@nmu.edu with any further questions regarding your rights as a participant, complaints, or concerns about this research. You can also call this number if you feel this study has harmed you.
8. **Payment for participation:** Participants will receive no payments for participation in this study.
9. **Voluntary Participation:** Your decision to be in this research is voluntary. You can stop at any time. You do not have to answer any questions you do not want to answer. Refusal to take part in or withdrawing from this study will involve no penalty or loss of benefits you would receive otherwise.

You must be 18 years of age or older to take part in this research study. If you agree to take part in this research study and the information outlined above, please sign your name and indicate the date below.

You will be given a copy of this consent form for your records.

Participant Signature

Date

Person Obtaining Consent

Date