Intermittent Hypoxia with Exercise, Voluntary Breathing, and Rest: Potential Benefits for Physical and Mental Performance, Injury Prevention, and Heart Rate Variability

Adrienne AJ Fisher

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American Public University

College of Health Sciences, Department of College and Health Sciences

Dr. Daniel G. Graetzer PhD

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Abstract

This article provides the reader with compelling evidence that intermittent hypoxic training (IHT) and intermittent hypoxic exposure (IHE) has a strong place as a non-pharmacological treatment strategy not only for diseases such as hypertension, diabetes, obesity, cardiovascular disease, osteoporosis, stroke and injuries such as spinal cord injury (SCI), but also for anti-aging, athletic potential and daily vitality. The reader is guided through a history of hypoxic conditioning and current day research in the field of IHT and IHE. Furthermore, the reader is presented with correlations between improvements in the aforementioned comorbidities and voluntary breath control such as slowing the frequency of the breath, forced exhalations and breath holds as a method of inducing hypoxia. A low lung volume breath-hold on an exhalation has been shown to be an effective method of inducing the frequency, intensity and duration of intermittent hypoxia necessary to achieve the published effective protocols to elicit beneficial results. Additionally, respiratory strength and lung function rapidly decline with age in line with the aging of the immune system, immunosenescence, and the musculoskeletal system, sarcopenia. Both breathing exercises and intermittent hypoxia combined have shown to have the therapeutic potential to improve the effects of aging both without exercise, and in conjunction with exercise, the combination of which have a strong potential for injury prevention, cognitive enhancement, anti-aging, non-pharmacological disease prevention and treatment, athletic improvement, and an improved heart rate variability with associated reductions in anxiety and depression. The parallels between intermittent hypoxia protocols and breathing exercises are striking. Therefore, these

parallels inspire the hypothesis that the combination of the protocols are superior to either independently. Additionally, there are many positive outcomes that fine-tuned breathing variables produce that strongly mimic those of intermittent hypoxia protocols. Inspired by the potential strength in interweaving the two modalities, in addition to a continuous pondering of a more convenient, low-cost strategy for implementing daily intermittent hypoxic routines, the author interweaves the benefits of voluntary breath-work and intermittent hypoxia to introduce and examine the possibility of a hypothetical Breath Induced Intermittent Hypoxic Training protocol, *BIIHT,* as a therapeutic intervention for improving chronic disease, athleticism, body composition, heart-rate variability, and optimized health and longevity.

Keywords: intermittent hypoxic training, intermittent hypoxic exposure, hypoxia, slow-breathing, voluntary apnea, voluntary breathing, beneficial hypoxia, forced exhalation, forced expiratory technique, residual volume, respiratory strength, total lung capacity, hypoxia inducible factor HIF-1, cognition, cardiovascular health, pranayama

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AD	Alzheimer’s disease
ANS	Autonomic nervous system
BIIHT	Breath induced intermittent hypoxic training
BDNF	Brain derived neurotrophic factor
CNS	Central nervous system
EPO	Erythropoietin
FEV	Forced expiratory volume
FRC	Functional residual capacity
FiO2	Fraction inspired oxygen
HIF-1	Hypoxia inducible factor
HIIT	High intensity interval training
IH	Intermittent hypoxia
IHE	Intermittent hypoxic exposure
IHT	Intermittent hypoxic training
NO	Nitric oxide
OST	Obstructive sleep apnea
OTS	Overtraining syndrome

PiO2	Partial pressure inspired oxygen
RV	Residual volume
SaO2	Oxygen saturation arterial blood
SpO2	Blood oxygen saturation pulse oximeter reading
TLC	Total lung capacity
TV	Tidal volume
VEGF	Vascular endothelial growth factor
VRF	Vascular risk factor

"Opportunity is missed by most people because it is dressed in overalls and looks like work."

- Thomas Edison

CHAPTER 1

INTRODUCTION

1.1 Global Health Crisis

Currently, there is a global health crisis that contributes to nearly 75% all deaths (Schmidt, 2016). The health crisis is chronic disease and immediate action needs to take place to improve the known preventable risk factors that contribute to the presence of chronic disease. Cardiovascular disease, pulmonary disease, type two diabetes, and cancer have dominated as the most deadly chronic diseases, and the majority of individuals globally are diagnosed with two or more of these comorbidities (Hajat & Stein, 2018). The risk factors that lead to the development of these comorbidities are obesity, hypertension and dyslipidemia (Fruh, 2017).

All three of the aforementioned risk factors can be controlled through proper diet, exercise, and other unique modalities such as intermittent hypoxic training and breath training such as pranayama, resisted inspiratory and expiratory training, and voluntary apnea is practiced in free diving and yoga (Naverrete-Opazo & Mitchell, 2014) Results-driven exercise and diet have been abundantly studied and published in the literature as preventative mechanisms for comorbidity risk-factors (Hellenius et al., 1993). Therefore, a sharp lens will be put on the benefits of intermittent hypoxia and breath training in conjunction with exercise as a modality for reducing chronic disease risk factors, which have the potential to reduce the rates of chronic disease alongside the coinciding global economic burden (Dale et al., 2015 & Yach et al., 2004).

What is the solution? Many are well aware that improvements in dietary choices and physical activity can have a profound effect on current functional capacity and longevity. Why don't we do it? The restrictions that are most common are lack of time, motivation, willingness to change, financial assistance, childcare and functional status. How do we increase motivation, lessen the financial burden, and expand time by increasing efficiency of exercise? The answer is: an exercise routine that is efficient, effective, and interesting. These are the factors that represent a high level of convenience, but also a recipe for consistency. By integrating a voluntary breath routine into a workout that makes the workout more effective and more efficient, while simultaneously enhancing feelings of calm and potentially enhancing health and longevity, would chronic disease numbers begin to fall (Russo et al., 2017)? If an athlete could gain an athletic advantage by implementing a voluntary breathing technique that not only enhances metabolic and neural markers, but also decreases the risk of injury through core activation, then this is a technique that could be employed by coaches for profound results (Ki et al., 2016).

Not only can a methodology that motivates a person to be less sedentary, one of the leading causes of the development of comorbidity risk-factors, resolve the epidemics of obesity, hypertension, and dyslipidemia, but it can also contribute to a more vital functional capacity, inclusive of community based activities that lead to less instances of anxiety and depression, two more risk factors predisposing a person to chronic disease (Booth et al., 2012; Voinov et al., 2013). The obese population may have more consistency in their exercise routine by incorporation of gentle techniques such as IHT (intermittent hypoxic training) and IHE (intermittent hypoxic exposure) with breathing exercises because of the enjoyment factor that is associated with sub-maximal vs maximal exercise, coinciding with less impact and subsequent joint pain. Furthermore, the lack of boredom that is typically associated with a repetitive and predictable exercise routine by integrating some novel therapies such as respiratory strength and intermittent hypoxic protocols could aid in retention of skill and consistency with a program (Cavuoto et al., 2016).

1.2 Intermittent Hypoxic Training & Intermittent Hypoxic Exposure

Intermittent hypoxic exposure (IHE) and intermittent hypoxic training (IHT) have been studied for over a century with altitude physiology dating back to the 1700s (West, 2016). Hypoxia is the lessening of oxygen within the organism that prevents proper functioning (Cafaro, 1960). Hypoxia has the ability to be highly damaging to the organism as is seen in the frequent and severe hypoxic apneas seen in OSA, obstructive sleep apnea, or it can be highly beneficial, as is seen out of labs at Harvard, Wayne State University, and the University of Florida’s McKnight Brain Institute, where individuals with spinal cord injuries are learning to move and breathe again using intermittent hypoxia protocols (Dale et al., 2015; Naverrete-Opazo & Mitchell, 2014).

When it comes to intermittent conditioning protocols, some ambiguity exists in the literature when referring to hypoxic training protocols (Verges et al., 2015). It is imperative that clarity is brought to the terminology that is used within the worlds of hypoxic conditioning in order to create a stable foundation upon which a deeper understanding can take place. Both intermittent hypoxic exposure, IHE, and intermittent hypoxic training, IHT, have piqued the interests of scientists for decades with a powerful surge in this then niche area in what was formally known as the Soviet Union, taking place in the hypobaric chambers that were built for acclimatizing Soviet pilots for the war in the 1930s. These Russian war pilots needed to be conditioned to fly up to 17,000ft above sea-level, which called for an intense hypoxic training protocol that proved effective (Serebrovkaya, 2002). Intermittent hypoxic exposure, IHE, is the passive exposure to lesser amounts of oxygen as a mechanism of either reduced partial pressure in the air or lower inspired oxygen, resulting in a lower arterial blood oxygen level (SaO2) such as that induced by voluntary or involuntary apnea (Lizamore et al., 2016). Intermittent hypoxic training, IHT, combines the concepts of IHE with endurance or strength training, which has been shown to be highly effective at improving athleticism, body composition, and health and longevity (Levine, 2002).

Both IHE and IHT have been shown to be extremely beneficial in the fields of non-pharmacological medicine and elite athletics (Serebrovska et al., 2016). IHE has the passive therapeutic benefit that an individual who has restricted movement capacity based on disease or injury can take advantage of. The ability to participate passively in a training regimen that does not require movements can benefit those whose have suffered from stroke, heart attack, sports injury or spinal cord injury (Mateika et al., 2014). There is a plethora of research on using IHE therapeutically for those who have suffered a spinal cord injury, SCI, to create improved motor plasticity through the generation of brain derived neurotrophic factor, BDNF, and serotonin as a means to create a window of movement potential in an area of the body that previously had limited or no movement due to the spinal injury (Wilkerson & Mitchell, 2009).

Not only have scientists, such as Dr. Gordon Mitchell, Dr. Jason Mateika, and Dr. Tatiana Serebrovska, studied the effects of long-term facilitation, LTF, or respiratory motor plasticity in those with spinal cord injuries, who previously have had a disconnect with respiration due to the spinal injury, but have also shown motor plasticity in other areas of the body such as improved locomotion Following IHE (Hayes et al., 2014; Schega et al., 2013). IHE has been shown to be effective at lowering blood pressure, regulating blood glucose, increasing insulin sensitivity, reducing body fat, improving bone density, and improving motor learning (Urdampilleta et al., 2012). Each of these will be elaborated on further in devoted subsections.

IHT is the combination of IHE and exercise. The exercise protocols that have been shown to be beneficial are inclusive of sub-maximal, maximal, and supra-maximal aerobic/anaerobic cardiovascular exercise in addition to strength training with a wide variety of hypoxic dosing along side the exercise routine (Czuba et al., 2018). Some studies have shown that strength training in an IHT style can produce higher levels of strength, muscle mass and lower body fat (Guardado et al., 2020). The mechanisms and theories on IHT strength training are further detailed in the section on athleticism devoted to this topic.

Obese individuals have been shown to have a greater improvements in body fat and muscle mass when performing light, sub-maximal exercise such as walking or cycling, while exposing themselves to hypoxia (Netzer et al., 2008). This has profound implications for an overweight individual who may otherwise have a hard time maintaining consistency with their exercise routine because of the strain on their joints and a lack of perception of enjoyment. Endurance athletes have been going to the mountains for decades with methods such as living high, training low, LHTL, a method that exposes the athlete to lower levels of oxygen while sleeping and performs their exercise training at sea level in order to perform maximally without the known cardiovascular and strength limitations that exercising in severe hypoxia can cause (Wilber et al., 2007). Athletes additionally have the option of performing their training in altitude tents, chambers, or wearing an altitude training mask while performing their exercise routine (Serebrovska et al., 2016). Athletes train at altitude in order to increase their levels of erythropoietin, EPO, a hormone secreted by the kidneys, which increases production of red blood cells in the bone marrow, increasing oxygen carrying capacity, strength and endurance (Płoszczyca et al., 2018). Not only are increased levels of a EPO in the system beneficial in terms of athletic performance, but it has also been shown to have a protective effect in relation to the heart and the brain (Sprick et al., 2019). Other athletic improvements include improved cellular buffering when performing high intensity exercise that can be beneficial for a hard charging athlete whose minuscule improvement in competition time can mean the difference between first and second place in a competition (Woorons et al., 2007). The athletic benefits of IHE and IHT will be discussed in further detail in the section devoted to this topic. See Figure 1 for the VO2 max improvements of a group training an IHT protocol.

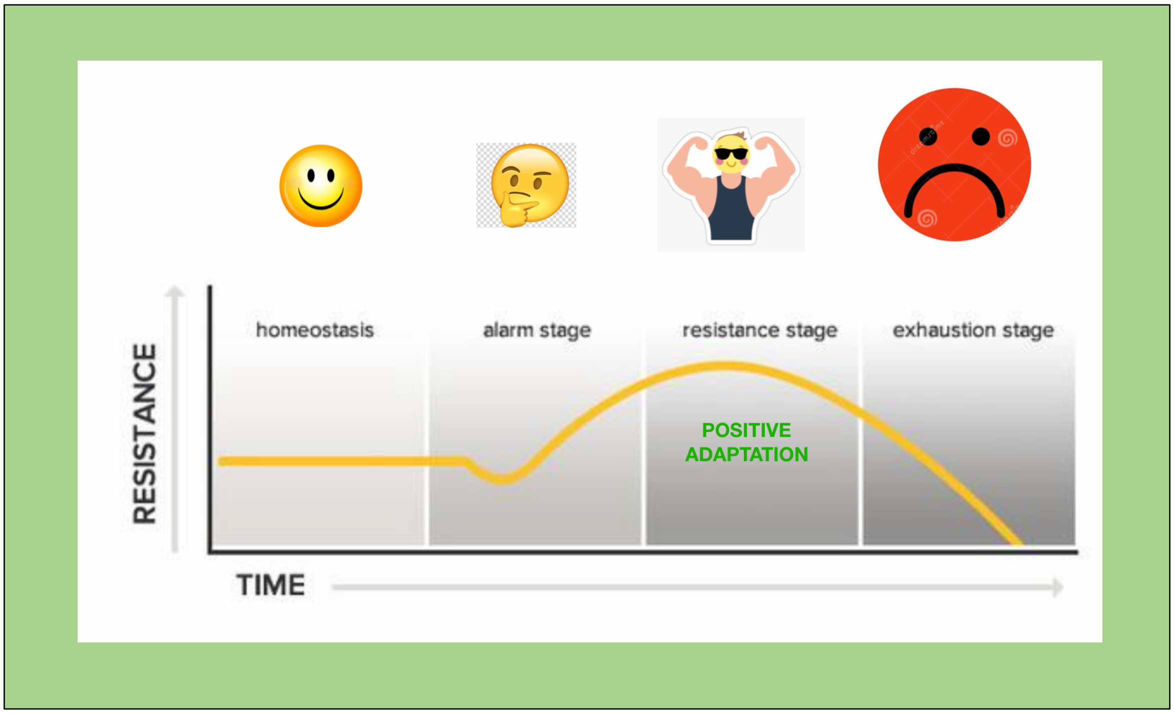
Figure 1

Variable	G-LH-TL		G-IHT		G-C	
	Before (x±SD)	After (x±SD)	Before (x±SD)	After (x±SD)	Before (x±SD)	After (x±SD)
WR_{max} (W)	370 ± 18.6	391*** ± 18.6	385 ± 29.2	410*** ± 37.2	370 ± 24.2	374 ± 21.8
WR_{LT}(W)	292 ±21.4	306* ±16.4	286 ± 25	308** ± 36.7	260 ± 21.1	268 ± 16.8
$VO_{2\ max}$ (l/min)	4.58 ± 0.3	4.81*** ± 0.34	4.55 ± 0.28	4.71*** ± 0.33	4.54 ± 0.23	4.54 ± 0.21
VO_{2max}(ml/kg/min)	66.0 ± 4.0	68.9*** ± 4.4	67.6 ± 2.7	69.9*** ± 1.4	67.0 ± 2.9	67.1 ± 2.7
VO_{2LT}(l/min)	3.86 ±0.29	4.12*** ±0.26	3.72 ± 0.20	4.06*** ± 0.41	3.5 ± 0.18	3.59 ± 0.15
VO_{2LT}(ml/kg/min)	55.9 ± 5.0	59.5*** ± 4.8	55.8 ± 3.5	60.0*** ± 1.6	51.6 ± 2.7	53.7 ± 3.0
VE_{max} (l/min)	165.1 ± 11.9	165.7 ± 12.7	169.6 ± 14.1	181.8*** ± 17.7	172.8 ± 14.5	169.8 ± 14.4
BF_{max} (1/min)	57.5 ± 3.9	58.8 ± 6	59.6 ± 6.5	65.0** ± 7.3	61.5 ± 7.2	60.4 ± 8.6
RER_{max}	1.09 ± 0.01	1.08 ± 0.02	1.09 ± 0.02	1.11*** ± 0.01	1.09 ± 0.01	1.09 ± 0.01
HR_{max} (bpm)	191 ± 3.1	192 ± 3.8	195 ± 5.1	192*** ± 3.7	196 ± 6.6	194 ± 4.9

Note: A comparison of 3 groups in 90 minute, 3 times per week training sessions, 1. LH-TL (live high-train low) 2. IHT (intermittent hypoxic training) 3. Control. Adapted from "Comparison of the effect of intermittent hypoxic training vs. the live high, train low strategy on aerobic capacity and sports performance in cyclists in normoxia.", by Czuba, M. et al., *Biology of sport*, *35*(1), 39–48. https://doi.org/10.5114/biolsport.2018.70750

1.3. Hans Selye, GAS, & Hormesis

Figure 2



Note: Han's Selye's General Adaptation Syndrome GAS. Adapted from "Selye's General Adaptation Syndrome [GAS]", by Ishak, I. (2020)., retrieved from https://hawkfitcoaching.com/blogs/news/selyes-general-adaptation-syndrome-gas

A history in the origin of the words distress and you stress is warranted is a preface To a dissertation that Aims To demonstrate The difference between intermittent hypoxia as a Beneficial stress (Eustace) and a detrimental stress (Distress). In Selye's most popular book, *The Stress of Life*, he coined the term distress and you stress and explains in detail general adaptation syndrome. the research of Hans Selye should be mentioned alongside the concept of hormesis. Hans Selye was a Hungarian endrocronologist and the founder of the General Adaptation Syndrome (Tan & Yip, 2018). The three stages of his GAS model are the alarm stage, the adaptation stage and the exhaustion stage, all of which represent how an organism responds to a stimulus in the environment (Sandor et al., 2017). In his book *The Stress of Life*, he deems a bad stress that an organism cannot adapt to a *distress*, and a beneficial stressor that an organism is able to adapt to a *eustress* (Tan & Yip, 2018). Hypoxic exposure can fall into the distress or the eustress category based on the dose.

It is the dose that matters with hypoxia, exercise, and even vitamins and minerals. Vitamin A in small doses is healthy, but in larger doses can cause seizures and death (Wooltorton, 2003). How much exercise do we need? How much hypoxia do we need? Both exercise and hypoxia are double-edged swords. Both have been shown to be highly beneficial in small doses as shown in Figure 1, but both can be very distressful for the organism at high doses because the organism is not able to adapt to the extreme doses of the stressor. There is literature that shows that ultra-marathon runners create so much reactive oxygen and nitrogen species without adequate recovery from their intense exercise, that their immune systems become dysregulated with constant occurrences of upper respiratory infections (Peters, 1983). Yet, small exercise doses trigger anti-oxidant defenses in response to the free radicals generated and strengthen the exerciser's anti-oxidant pathways, so that they are more able to adapt to free radicals in the future (Kouda, 2010).

Katsuyasu Kouda defines hormesis as a low dose stimulant for a high dose positive response that produces long-term health benefits through the adaptation to the initial stressor. A smartly planned exercise routine with adequate rest or acute intermittent hypoxia would be examples of hormesis. Large doses of either of these would cause *distress*. In Michael Schieber's thesis for Northwestern University, he describes the longevity effects on *c. elegans* when exposed to hypoxia. He describes the hormetic effects of the cells being deprived intermittently of oxygen and leads the reader through a scientific background of the benefits of exposing an organism to reactive oxygen and nitrogen species, but only at a small dose (Schieber, 2001). Schieber went on to perform years of research on life extension and oxygen sensing such as his partnership with Chandel on the study that showed longevity associated with oxygen deprivation (Schieber & Chandel, 2014). Mark Mattson at the National Institute on Aging in Baltimore, MD, also commented on hormesis, including descriptions of the adaptive stress response and preconditioning (Mattson, 2008). The main focus of his research at his laboratory is potential hormetic responses to stimuli. He showed in an earlier study that calorie restriction is an effective method at reducing the risk of cognitive decline (Mattson, 2000). Therefore, even food is a stressor. Consume too much, and one will suffer the distressful consequences. Ultimately, the dose-response relationship is so sensitive, and this is why further research is needed to clarify the dosing of acute intermittent hypoxia combined with passive exposure (IHE) and exercise (IHT). Additionally, the potential of using a combination of hypoventilation, forced exhalation and breath-retention, in order to not only reap the rewards of improved core function, motor learning and general health, but also implement doses of intermittent hypoxia, could be a highly convenient and HRV-improving method of employing acute doses of hypoxia.

Programs inclusive of a combination of breath-training, exercise and intermittent hypoxia have both short-term and long-term positive outcomes that can be categorized using the S-M-A-R-T method, which states that the short and long-term goals of a program are S-smart, M-measurable, A-attainable, R-relevant, and T-time-based (Seguin, Epping, Buchner, Bloch, & Nelson, 2002). Specifically, the short-term goal of being consistent on a strength training program for a period of 12 months with a new breathing routine in conjunction with hypoxia (IHT) is not only feasible, but more likely to support consistency because of the research-driven results of working out in hypoxia and preventing injury in the new-trainee population through implementation of a core-recruiting breathing technique (Ishida et al., 2017). In the long-term, the potential increases in muscle mass and fat-loss in comparison to the same workout in normoxia (normal oxygen level) will continue to engender motivation to continue making progress (Guardado et al., 2020). The measurable effects of the short-term hematological, metabolic, and vascular improvements, such as increases in red blood cells and lowering of blood pressure, have been well documented, and the long-term body composition and blood lipid improvements will elicit positive reinforcement from patients' doctors (Serebrovskaya et al., 2016). The short and long-term goals of becoming adapted to an IHE or IHT program are attainable by most because of the low-risk nature of these protocols, as long as the hypoxic training is not contraindicated by a doctor (Naverrete-Opazo & Mitchell, 2014). Incorporation of intermittent hypoxia into a training routine is highly relevant to not only short-term health and vitality, but also long-term strength and longevity (Mattson et al, 2008). The time-based component of the SMART method is represented well by the specific prescriptions of acute and moderate doses of the intermittent hypoxic training protocols that can be very efficient in the time that it takes to get a training adaptation. Because of the decreased amount of time that it takes to get a training effect because of the increases in anaerobic metabolism and energy expended during and after exercise, it is a highly efficient method that allows the trainee to use minimum effective dose for maximum effect while reducing the exercise session volume-load on the joints (Guardado et al., 2020; Netzer et al., 2007; Woorons et al., 2017). A time-efficient approach of 2-3 times per week training with positive results has the ability to inspire a big percentage of the population to not only embark on, but also continue a hypoxic training protocol. A combination of IHT, IHE and breath-training has the ability to specifically, measurably, attainably, relevantly, and in a time-based manner flesh-out many areas of short and long-term goals for prospective trainees. Because short and long-term goals have been shown conclusively to be key cornerstones in results-driven success through retention of motor skills and consistency with a program, intermittent hypoxia and breath-training may have strong legs to stand on in the world of therapeutic exercise for both the athletic and the general population (Corrêa & de Souza, 2009).

1.4 Covid-19 and Hypoxic Conditioning Protocols

To conclude the introductory statements, there have been a handful of recent reviews on the hypothetical application of the preventative and therapeutic mechanisms for the current pandemic of Covid-19. The reader should be made aware of the potential application of intermittent hypoxia, both IHE and IHT, as a potential mechanism to assist in a post Covid-19 world, in which the virus and its variants still exists, and many other viruses that act in a similar manner could be fought against through a more effective preventative strategy.

Even though several vaccines have been successfully implemented and the number of cases around the world have declined significantly, there is still a large portion of the global population who have not been vaccinated due to belief systems, illness, or unavailability (Haidere et al., 2021). It has been suggested that utilizing the “pre-conditioning” effect of intermittent hypoxia that has been effectively implemented for preventing the severity of cardiac infarction, stroke, and lung injury due to COPD, asthma and emphysema, could be an effective mechanism of preventing the depth of the Covid-19 injury to the lungs, kidneys, heart and epithelium of the vascular walls (Hertzog et al., 2021). Due to IHT’s activation of HIF-1 that then encodes downstream targets such as VEGF and adenosine, there is the potential for a reduction in the amount of ACE-2 receptors that the Covid-19 virus can attach onto because of the pathways of activation of the adenosine molecule that eliminate some of the ACE-2 receptors (Serebrovska et al., 2020). Those who live at high altitude have less ACE-2 receptors because of the upregulated HIF-1 molecules that then downregulate ACE-2 receptors, and many groups at altitude have shown significantly less cases of Covid 19 (Segovia-Juarez et al., 2020). This mechanism of an increase in adenosine, a vasodilator, encoded by HIF-1 that lessens the amount of ACE-2 receptors in the lungs is at play in both IHE and IHT (Hertzog et al., 2021).

Additionally, the activation of anti-oxidant pathways through HIF-1 may have the ability to reduce the cytokine storm that can happen as a result of the virus as it has been shown that exposure to hypoxia has had the ability to reduce levels of pro-inflammatory cytokines such as Il-4 and Tnf-*a* (Serebrovska et al., 2020). Furthermore, the pre-conditioning effect with acute doses of hypoxic exposure has been used as a preventative mechanism to upregulate factors such as VEGF, EPO, and antioxidant enzymes that produce increased blood vessels for increased blood flow and tissue oxygenation, which decreases inflammation, macrophage entry, and tissue/cell death (apoptosis) (Cai et al., 2021). Because of intermittent hypoxia's great potential as a strategy to aid in this current pandemic and those that may occur in the future, this is an area that direly needs attention and much more research is needed to envisage a future in which more low-risk therapeutic options are well-researched and available.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

The term hypoxia has been associated with chronic disease states such as sleep apnea and chronic pulmonary disorder (Dewan et al., 2017). How could exposing oneself to hypoxia be beneficial when it has been shown in many studies to be associated with inflammation and chronic disease? For example, it has been shown that it is the severity and frequency of the hypoxia that a subject with Obstructive Sleep Apnea is exposed to that predisposes them to a state of high reactive oxygen species such as NOS1 that contributes to hypertension (Lavie, 2015). Furthermore, extreme altitude exposure and the subsequent exposure to extreme low SpO2 levels (lower than 70%) have also been associated with excessive free radical production that predispose a person to a host of chronic diseases (Vold et al., 2015). Many authors began to question: what is the difference in dose between good and bad hypoxia? In a review by Malshe, the author reinforces that acute intermittent hypoxia has been shown to be highly beneficial on many physiological levels including improved endurance and reduced incidence of chronic disease (Malshe, 2011).

The known benefits of hypoventilation, breath retention and forced exhalation have been well documented in the literature and will be highlighted in this literature review. Intermittent Hypoxic Training (IHT) has been documented in the literature beginning after the performance enhancement of the Olympic athletes after the 1968 Olympics in Mexico City (Park et al., 2018). Before this time, there is a long history of research around the world, with an emphasis in Russia, Germany, and France, on the physiological effects of altitude exposure/training. Altitude simulation using oxygen mixtures in chambers less than the 21% that humans breath in the Earth's atmosphere began to be used to a high degree in Russian research in the early and mid-

1900's (Serebrovskaya, 2002). French physiologist and professor Xavier Woorons has shown through a plethora of research that hypoventilation and breath retention while performing high intensity exercise can lead to changes in physiology during and after exercise that could give an athlete a competitive advantage (Woorons et al., 2020). The missing link in the literature is: with strategic protocols of acute hypoxia induced by a specific voluntary breathing methods, could we enhance cognition, core strength, motor learning, athletic markers, and health and longevity? What is the cross-link between the plethora of research on Intermittent Hypoxic Training and the research on hypoventilation and breath retention? How does the research on Acute Intermittent Hypoxia in terms of motor plasticity tie into breath training with the potential to improve core function through not only breath manipulation, but also improved motor learning through exposure to intermittent hypoxia? How does the concept of hormesis apply to the world of breath training and hypoxia? This literature review will provide a backbone to exploring these questions further in order to solidify stronger connections between these well-researched areas.

2.2 Intermittent Hypoxia – From It's Birth to a US History

Hypoxia is defined as low oxygen levels in the biological tissues of the organism (Michiels, 2004). The word hypoxia has been prevalent in the literature since the year 1938, but it was the word "anoxia" that was used to describe a biological tissue deprived of oxygen prior to this (Richalet, 2021). Jean Paul Richalet, as one of the head researchers in the area of hypoxic research, wrote a history on the words anoxia and hypoxia within the global literature, and within this review, Richalet brings to the reader's attention the potential hormetic features of the current use of hypoxia in that a short exposure could lead to positive adaptations, whereas anoxia is a detrimental and non-life sustaining deprivation of oxygen that pushes an organism into the exhaustion stage of Selye's General Adaptation Syndrome Model.

In a historical article honoring the life and research of French physiologist Paul Bert, author Rudolph (1993) reinforces to the reader that Paul Bert was the founding father of altitude physiology as he created the law of partial pressure at altitude in 1878 and the subsequent effects that these partial pressures had on organisms. Over half a century later, the Teppermans' research showed up in the literature and presented the conclusions that the blood lactate levels of athletes was higher post exercise at altitude than at sea levels (Tepperman, 1948). This mid-twentieth century study led the way for future research in the United States such as that of a Colorado physiologist and professor, John Weil, whose research team analyzed a group of natives living in Leadville, CO and compared them to a lower altitude group (Weil et al., 1971). The group of authors found that the chemoreceptor response was attenuated in the individuals exposed to higher altitude. The following two decades in the United States brought forth a plethora of research on the topic of hypoxia, laying the ground work for scientists Gregg Leonard Semanza, John Ratcliffe and William Kaelin Jr. to win the Nobel prize based on their outstanding achievements in the area of oxygen research and HIF, hypoxia inducible factor, disentangling how a cell senses oxygen (Prabhakar, 2020).

John Reeves was also instrumental in the world of altitude exposure, himself a resident and professor in Colorado after completing years of fellowship studying the effects of hypoxia on cattle. Voelkel and colleagues, which Reeves was one, found that hypoxia impaired vasodilation in the lung tissue (Voelkel et al., 1981). This was an example of a scientist who started out his career experimenting with the results of an extreme exposure to a stressor (chronic/severe hypoxia). He worked in labs, in which the subjects were exposed to extreme high altitudes for long periods of time, which produced poor results and consistent distress in the organisms. It was twenty years later in 2002 that Reeves began to look at the hormetic side of hypoxia in his published paper discussing the difference between beneficial acute hypoxia and distressful chronic hypoxia (Reeves, 2002). Many other scientists followed this path, in which they spent several decades analyzing the negative effects of hypoxia on the system, such as the cornucopia of research on the area of sleep apnea, before they began to ask the question of dose in terms of a possible beneficial response. For example, Crawford et al. (1991) found that markers of atherosclerosis were elevated with exposure to chronic and severe hypoxia, yet with current acute hypoxia research, we now are starting to delineate a difference between "good" and "bad" hypoxia. Naverrette- Opazo, in her review on the therapeutic potentials of acute intermittent hypoxia, she categorizes hypoxia that causes pathology to be between 2-8% inspired oxygen and between 42-2,400 episodes per day. Beneficial hypoxic episodes tend to range between 9-16% inspired oxygen and 3-15 episodes per day (Navarrete-Opazo, & Mitchell, 2014).

It was the turn of the 20th century that brought forth Gordon Mitchell (who collaborated with Navarrete-Opazo in the aforementioned review paper). His research on the beneficial effects of acute intermittent hypoxia begins to populate the literature in 1999, during which he leads the research with Richard Kinkead on the improved plasticity of respiratory motor neurons in response to acute doses of hypoxia (Kinkead & Mitchell, 1999). This leads to Gordon Mitchell joining the McKnight Brain Institute as part of the University of Florida, where he has been conducting research and mentoring PhD students in the field of intermittent hypoxic research and spinal cord injuries ever since. He has published many papers while at the McKnight lab, including research on disentangling the underlying mechanisms of compensation in ventilation mechanics after spinal cord injury, which will lead to future research on how to target and strengthen these mechanisms through intermittent hypoxic exposure in order to improve respiratory motor neuron plasticity (Johnson & Mitchell, 2013). In line with Mitchell's findings, Randy Trumbower at Harvard University witnessed an improvement in hand motor skills when exposed to moderate doses of hypoxia for short durations after spinal cord injury (Trumbower et al., 2017).

Todd Astorino was also groundbreaking in this field of research. He wrote his dissertation at the University of New Mexico, in which explores the effects of hyperoxia on VO2 max, and shows that there is a linear relationship between an increase in oxygen and VO2 max (Astorino, 2001). This interest in oxygen research, led him to participate in research on heat acclimatization when exposed to hypoxia. They determined that there is no positive effect, but also that it is not detrimental to heat acclimatize during hypoxic exposure (White et al., 2016). Another leading institution in the field of hypoxic research is Case Western University. David Kline's dissertation, born out of this university, supporting the idea that Nitric Oxide is a regulator in ventilation during hypoxia led to future research in the area of intermittent hypoxia (Kline, 2000). In 2007, Kline and a team of researchers show how the homeostatic mechanisms of ventilation, when exposed to hypoxia, contribute to plasticity (Kline et al., 2007).

2.3 Intermittent Hypoxia Internationally

It was the Olympics of 1968 in Mexico City at an elevation of 8000 feet, after which athletes experienced gains in their performance, but also experienced declines in their performance during the games, that intrigued scientists and lead to a spike in the area of altitude research (Malshe, 2011). Moving back to a period about 4 decades prior in Russia, represents one of the first surges in interest in the area of hypoxic research. The Soviet Barometric Laboratory at the

Leningrad Military Academy was developed for the purpose of conditioning pilots who needed to fly at heights of 17,000 feet (Serebrovskaya, 2002). It was here that a plethora of research began to take place on not only pilots, but individuals suffering with obesity, asthma, and other chronic ailments.

The Buteyko Method was born in Russia in the mid-twentieth century, and several asthma studies were conducted at the Leningrad Military Academy. The Buteyko Method was developed by Konstantin Buteyko. He suggested slowing the breath down (hypoventilation) and holding the breath as a means of therapy for asthmatic patients and COPD (Vagedes et al., 2021). A recent randomized controlled trial showed that Buteyko Breathing is more effective than Pranayama breathing on improved quality of life in asthmatic patients (Prem et al., 2013). Recent research has shown that the Buteyko Method has the potential to lower blood SpO_2 levels and therefore affect the carbon dioxide levels in the body with the slow breathing and breath holds. Ultimately, this leads to a reduced chemosensitivity in the chemoreceptors, which is a positive adaptation for those who have lung disorders (Courtney, 2020). More research needs to be done in this area, in which we explore a form of Buteyko breathing as a method to induce acute beneficial doses of hypoxia that improve plasticity, athleticism, and a state of calm through up-regulation of the vagus nerve as has been shown in slow breathing research (Russo et al., 2017).

A method of achieving hypoxia through breath-work is a combination of hypoventilation and breath retention. Because a slow breath and breath retention (hypoventilation) causes a person to have a lower respiration rate, documenting the literature highlighting the multitude of benefits of slow breathing is warranted. Labord et al. (2019) showed an improvement in heart-rate variability (HRV) and sleep quality after 30 days of deep breathing exercises vs. social media use. Furthermore, Komori (2018) showed that slow breathing up-regulates the vagus nerve and causes parasympathetic dominance, strengthening the hypothesis that slow breathing increases relaxation through an increase in vagal tone. The Buteyko Method and research coming out of countries around the world all demonstrate the massive health benefits of slowly breathing at a rate of 6 breaths per minute vs rapid shallow breathing (Russo et al., 2017). Dovetailing the worlds of intermittent hypoxia with the well-known health benefits of slowing the breathing and breath retention could be a highly effective method of training the parasympathetic nervous system in conjunction with exposing oneself to acute bouts of beneficial hypoxia.

It was the French physiologist, Xavier Woorons , who has been groundbreaking in the area of combining hypoventilation and breath retention with high intensity exercise. He is member of the Association for Research and Promotion of Hypoventilation Training (ARPEH), which Emil Zatopek, the famed Czech athlete, who included hypoventilation training into his program as part of his success, was a member. Woorons has been the most prolific scientist in the area of hypoventilation training. Several of his studies show that inducing hypoxia in the body with exhalations to end residual volume (RV) is a key component of the recipe for inducing positive adaptations during exercise such as cellular buffering. In several studies, his team of researchers has witnessed up-regulation of glycolytic metabolism and increases in lactate production (Woorons et al., 2010). Woorons mentions that conditioning oneself to be able to cellularly buffer when performing high intensity exercise by exposing oneself to lowering ph levels, increased lactate and hydrogen ion production, has the ability to create even greater athletes who need to be their fastest and strongest as they work mainly in their anaerobic glycolytic state in competition (Woorons et al., 2020). An important study in conjunction with other leaders in the field, Millard, Pichon, Duvallet, Richalet, and Lamberto, concluded that prolonged expiration down to RV (residual volume) leads to arterial hypoxemia during submaximal exercise

(Woorons et al., 2007). The low levels notated in this study (70% SpO2) mimics those that are experienced during hypoxia (Naverrette-Opazo and Mitchell, 2014). In another study, Woorons studies athletes performing high intensity exercise while exhaling to a low pulmonary lung volume with breath retention (Woorons et al., 2019). The researchers found that there was an increase in glycolytic metabolism in addition to improved performance over the timed trial. His research has shown to have profound effects on improvements of athletes' performance in sprints, swimming, and Wingate test (Woorons et al. 2010). Is it feasible for the average exerciser to perform their intervals on a breath-hold? Is it safe? Due to the potential fainting and increase in blood pressure, it seems more advisable to only perform breath-holds and hypoventilation when performing sub-maximal exercise unless supervised by a professional physiologist (Parkes et al., 2014).

Nikolaus Netzer, an Austrian scientist, published a prolific portfolio of work focusing on the effects of intermittent hypoxia on several diseases, including obesity. In 2017, he co-authors on a research review that educates the reader on the line between beneficial and detrimental in the area of fat metabolism. Netzer shows in an earlier paper that sub-maximal exercise performed in hypoxia results in more fat loss than the sub-maximal exercise performed in normoxia (Netzer et al., 2007). The increase in the hormone leptin and the increased rate of lipolysis when exposed to hypoxia has been shown in many studies (Netzer et al., 2017). The most beneficial dosing is yet to be elucidated.

Gregoire Millet is a scientist based in Switzerland, who has been a pioneer and leader in the field of intermittent hypoxic training. He co-authored a 2016 review that educates the reader on the benefits of training in hypoxia including improved blood pressure, body composition and chronic disease mitigation (Millet et al., 2016). Recognizing the exercise limitations of an obese individual, Millet partnered with Olivier Girard and other leaders in the field to show that individuals suffering from obesity lose more body fat when walking while exposed to hypoxia (Girard et al., 2017). Furthermore, Camacho-Cardenosa et al. (2018) found that obese individuals performing HIIT in hypoxia lost more body fat than those performing it in normoxia. Is this a method for reducing the needed number of repetitions to achieve an adequate adaptation in the body without pushing the body into an exhaustion phase of the GAS model? The implications are profound.

2.4 Diving Deeper into Breath Manipulation

Looking deeper into the world of breath manipulation, the potential hypoxic benefits of performing Nisshesha rechaka pranaymana were reviewed by Malshe in 2011, in which he not only details his personal journey as a scientist with this form of pranayama, but also speaks of the wide range of health benefits when exposing oneself to mild doses of hypoxia. Malshe explains that slow exhalation breath leading to breath retention can bring the SpO2 levels down adequately to provoke adaptations in the body. Dr. Malshe out of the Antar Prakash Center for Yoga in India has performed several experiments on himself, which he has published on YouTube that show his SpO2 levels decline to as low as 70% SpO2 (Malshe, 2009). Malshe speaks of the potential red blood cell, hemoglobin and EPO production benefits of exhaling to a point of breath retention, but more research is needed to make the connection between holding one’s breath and experiencing the benefits of acute hypoxic conditioning. Costalat in 2013 showed that a diver’s breath hold can achieve the SpO2 levels necessary to induce a spike in HIF-1 levels with paralleling spikes in EPO (erythropoietin), which mirrors that of an athlete during altitude training or hypoxic chamber exposure. The Wim Hof Method is a current popular method that uses a combination of hyperventilation and breath holds to achieve the touted benefits of an improved immune system and a state of calm. Knox et al. (2014) showed that the Wim Hof style breathing method is able to increase levels of epinephrine and therefore attenuate levels of pro-inflammatory cytokines in the system.

In terms of motor skills improvement with breath manipulation, slow breathing in conjunction with training has shown improvements in this area. In a study integrating deep breathing with motor skill learning, improved cognition was confirmed through better retention of motor skills when performing slow breathing within the session (Yadav & Mutha, 2016). If an exerciser performs slow breathing that intermittently induces acute hypoxia, could this be a potential to receive the learning benefits of motor neuron plasticity in addition to the motor skill retention that is found through up-regulation of a calm and centered individual through improved vagal tone? These are the questions that need to be explored further.

In the world of injury prevention, in addition to the aforementioned improved motor skill learning, there is a plethora of research that shows that using a forceful exhalation or a bracing of the abs with an exhale or grunt can reduce pressure on the spinal segments (Stokes et al., 2011). Using various forms of forced exhalations or shouting mechanisms while working out has also been shown in a variety of literature to be able to improve low back pain and improve mechanics. For example, O'Connell (2013) showed that a tennis serve and forehand velocities are improved in those players who are allowed to grunt, which is a forceful exhalation. The coupling of resisted exhalations in conjunction with exercise has been of high interest in the Korean scientific community. Oh et al. (2020) found that women who performed the abdominal draw-in maneuver (ADIM) while performing a resisted exhalation had less low back pain and more core activation than those who did not. Another study out of Korea in 2015 showed that a forced exhalation in combination with core exercises was superior for deep core activation as demonstrated with EMG device to detect strength of muscle contraction (Park et al., 2015). If performing a forceful exhalation, could bring you to a low lung volume, this could could be a potential mechanism to not only induce acute bouts of hypoxia for motor skill retention, but also could prevent injury through improved activation of core musculature.

2.5 Conclusion

The vast amount of literature in support of utilization of IHE, IHT and respiratory training is indicative that these low-risk tools have a therapeutic place as part of a protocol that can act as a preventative tool or a therapeutic strategy for chronic disease. The current day researchers in these areas are enabling those with spinal cord injuries to move where movement was not an option, the obese to lose previously immobile body-fat and those with cognitive decline experience improved neural activity (Naverrete-Opazo & Mitchell, 2014; Netzer et al., 2008). More research needs to be done on healthy populations to test the efficacy of these strategies in areas such as enhanced cognition for motor learning and IQ, body composition changes, and anti-aging mechanisms such as prevention of osteoporosis, sarcopenia, immunosenescence and cognitive decline (Aiello et al., 2019).

CHAPTER 3

HIF-1 & OBSTRUCTIVE SLEEP APNEA

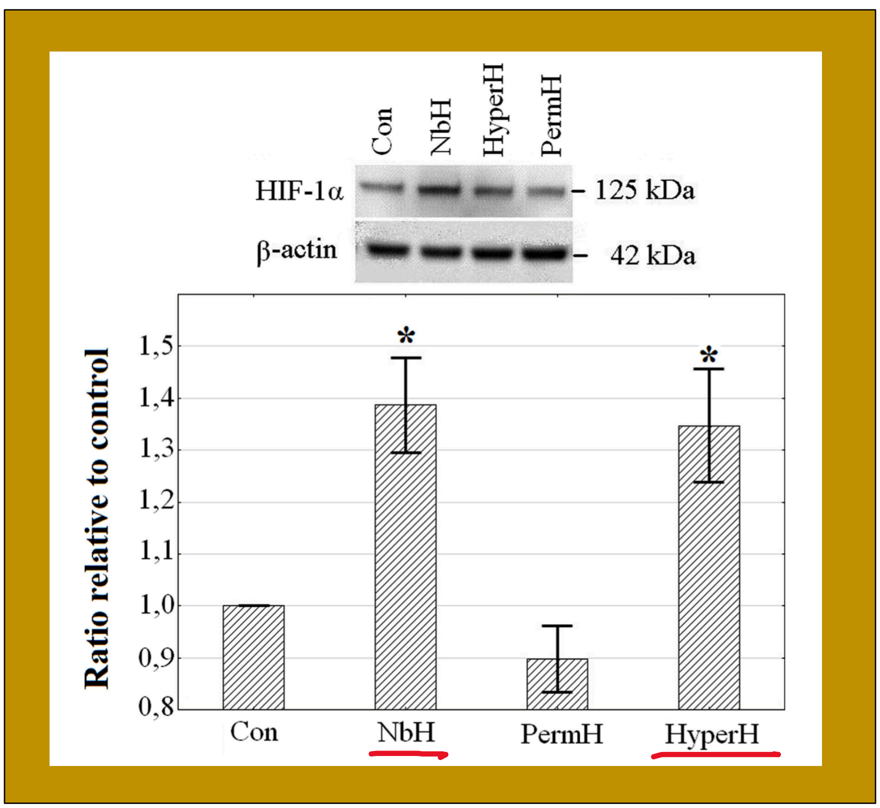
3.1 HIF-1 Defined

HIF-1, hypoxia inducible factor, is a transcriptional factor that is the master regulator of genes that are translated under hypoxia or low oxygen (Dale et al., 2014). Levels of HIF-1 increase under low oxygen whether that is the result of a low FiO2 or during apnea (Hellwig-Bürgel, 2005). FiO2 is the fraction of inspired oxygen in the air, which is 21% at sea level and slowly lowers as the altitude increases above sea level, where the air becomes "thinner", and the body has to work harder to inspire oxygen (Fuentes & Chowdhury, 2021). This is when HIF-1 increases in every tissue in the body in order to survive with less oxygen by increasing EPO, erythropoietin, in the bone marrow to create more red blood cells to have a bigger oxygen carrying capacity through the increased numbers of hemoglobin in the red blood cells (Haas, 2013). Athletes have been climbing mountains for years to take advantage of the increases in aerobic capacity due to this increase in red blood cells and some have artificially "doped" EPO to have a competitive edge, but this is now tested for and banned by the Word Anti-Doping Agency (WADA) (Handelsman, 2020).

An apnea is a breath hold, and it can be performed voluntarily, as in a free-diver's breath hold, or involuntarily, as in the stopping of breath during obstructive sleep apnea, OSA (Spicuzza et al., 2015). Holding the breath can result in hypercapnia, which is the abnormal elevation of CO2 in the blood with an associated drop in blood pH (Masterson, 2015). Hypercapnia can cause raised levels of HIF-1, which means that holding the breath can translate hypoxic genes that help the body search for and retrieve more oxygen for the body's tissues (Haas, 2013). Hypoxic genes are transcribed after HIF-1 is sent to the nucleus and then encodes the following factors that act as precursors for angiogenesis, increased red blood cell production and glycolytic metabolism: EPO, VEGF, BDNF, inducible nitric oxide synthase, lactate dehydrogenase A, phosphofructokinase I, and phosphoglycerate kinase 1 (Semenza et al., 1997).

As the reader is lead through the the following examination of the benefits of intermittent hypoxia, respiration strength, and where the two worlds dovetail, the question that remains is: can a person cause enough of an increase in systemic HIF-1 with a voluntary breath regimen, inclusive of slow breathing, forced exhales and breath holds to induce even a fraction of the positive effects that have been well researched in the areas of of intermittent hypoxia? OSA, obstructive sleep apnea, has shown extremely high levels of HIF-1 as a result of the excessive high number of involuntary apneas, taking place on average every 30 seconds, for 8 hours per night (Prabhakar et al., 2020).

Figure 3



Note: Increase in HIF-1 in both the hypoxic (NbH) and the hypercapnia group (HyperH). Adapted from "Hypercapnia potentiates HIF-1α activation in the brain of rats exposed to intermittent hypoxia.", by Tregub, P., Malinovskaya, N., Morgun, A., Osipova, E., Kulikov, V., Kuzovkov, D., & Kovzelev, P. (2020). Respiratory Physiology & Neurobiology, 278, 103442–103442. https://doi.org/10.1016/j.resp.2020.103442

Therefore, it is confirmed that a breath hold can induce HIF-1, but what is the minimum effective dose to elicit a positive adaptation through HIF-1 as a hormetic stressor instead of a maladaptive one as would be seen in a sleep apnea patient, who is holding their breath 30 seconds once a minute for 8 hours each night (Sforza & Roche, 2016)? These involuntary nightly breath holds that disrupt sleep are too much for the organism to recover from, which pushes the organism into Selye's exhaustion phase (Selye, 1950). Breath-hold training has been shown to reduce oxidative stress and reduce the response to hypoxemia in the blood (Joulia et al., 2003). Static and dynamic maximum voluntary apneas have shown high levels of EPO, induced by HIF-1, up to 17% for several hours following the last breath hold (Kjeld et al., 2017). These tests were done on elite, competitive breath-holders and free divers who hold their breath for several minutes. It is not necessarily feasible for an everyday exerciser to incorporate these lengthy voluntary apneas into their daily routine, but a competitively long breath-hold may not be needed to induce adaptation. Research here is needed on disentangling what the minimum effective dose is. See figure 6 for EP concentration during both hypoxia and hypercapnia.

Is there a breath routine, that is more moderate, that also raises levels of HIF-1 and the beneficial growth and glycolytic factors it encodes? Is there a breath routine that could be incorporated into a person's workout routine that spikes levels of HIF-1 in a healthy, hormetic way, with plenty of recovery in between, so that Selye's adaption phase can be taken advantage of fully? These are questions that need to be answered through future research. Answers to these questions would give the gift of convenience to individuals around the globe, who would like to utilize the benefits of acutely spiking their levels of HIF-1, but do not have the extra time or money to travel to a hypoxic chamber or up a high mountain. Throughout this exploration of the cross-link between the benefits of intermittent hypoxia and breath training, the concepts of HIF-1 and the genes that it encodes will be further elucidated on.

3.2 Obstructive Sleep Apnea – a Detrimental Dose

There is an abundance of a literature that makes the connection between the severe, acute, intermittent hypoxia that is experienced during the apneas of obstructive sleep apnea (OSA) and comorbiditie (Lavie, 2009). OSA sufferers experience anywhere between 40 to 40,000 apnea events over the course of the night whereas documented beneficial doses are far less frequent, intense and enduring (Navarrete & Mitchell, 2014) The high frequency, severity, and duration of apneic, hypoxic episodes, that are characteristic of OSA, push the organism into distress and the exhaustion stage of the general adaptation syndrome, causing systemic inflammation and subsequent chronic disease with a chronically activated sympathetic nervous system that contribute to higher levels of anxiety, depression, and muscle dysfunction (Gonzaga et al., 2015; Loredo et al., 1999).

An analogy can be made between high intensity interval training (HIIT) and intermittent hypoxia. What kind of an adaptation would be expected if an individual performed a high intensity (90-100% maximum heart rate) sprint drill, in which a rest to work ratio of 30 seconds work: 30 seconds rest was executed for 8 hours every night incessantly?

Not only would this be highly distressful on the musculoskeletal and nervous system due to inadequate rest, but it has been shown that disturbance of sleep is one of the leading causes of all-cause mortality (Garbarino et al., 2016; Medic et al., 2017). Not only is systemic inflammation and immunosuppression prevalent in those who are chronically sleep deprived, but these conditions also exist in ultramarathon runners, who have chronically elevated incidences of upper respiratory chest infection due to inadequate recovery time from frequent, intense, and extremely long training sessions (Žákovská et al., 2017).

Likening the high frequency, intensity, and duration of the intermittent hypoxic episodes caused by the frequent and severe apneas in OSA to frequent, intense, and long training sessions without recovery helps to bring clarity in differentiating between harmful doses of hypoxia and beneficial doses. An abundance of literature has shown that HIIT is effective in improving VO2 max, muscle mass, blood sugar, insulin sensitivity, amongst a list health benefits that improves not only athleticism, but health and longevity (Alarcón-Gómez et al., 2021; Marcinko et al., 2015) . Typical dosing for high intensity interval training ranges from 15 seconds to several minutes of high-intensity work, to an adequate rest load. It is recommended that high intensity sessions last between 20 and 90 minutes and are performed no more than three or four times a week (García-De Frutos et al. 2021; Viana et al., 2019). This integrates necessary recovery for the individual, as it is in the rest period during which positive adaptations in the musculoskeletal and nervous system take place (Morgan et al., 2015; Zając et al., 2015). Without the adequate amount of rest, the organism could certainly be pushed into over-training syndrome (OTS) or injury, which could take several months or years to recover from (Meeusen et al., 2013).

The dosing of intermittent hypoxia parallels that of high intensity exercise, which adheres to the school of thought of “minimum effective dose for maximum effective benefit”. The current recommendations of intermittent hypoxia training based on a cornucopia of research over the past several decades show that prescribed dosing can be as low as 15 seconds of exposure to either a prescribed percent oxygen inspired, FiO2, or arterial blood oxygen saturation levels, SaO2, as read on a pulse oximeter, SpO2 (Naverrete & Mitchell, 2014). Both titration of FiO2 and SpO2 readings have proven to be effective methods in eliciting beneficial outcomes, although some argue that looking at SpO2 readings may be a more effective method as there has been shown to be a high inter-individual variability in the dose response relationship (Soo et al., 2020). There is a large variation as to how individuals respond to various FiO2 levels, but most have found an effective FiO2 to receive enough of a response without moving into a maladaptive phase is 14-16% FiO2 or approximately 2500 meters above sea level (Ahluwalia & Underwood, 2021; Bärtsch & Saltin, 2008; Vardy et al., 2006). For clarity on how FiO2 percentages compares to altitude levels, see Table 2.

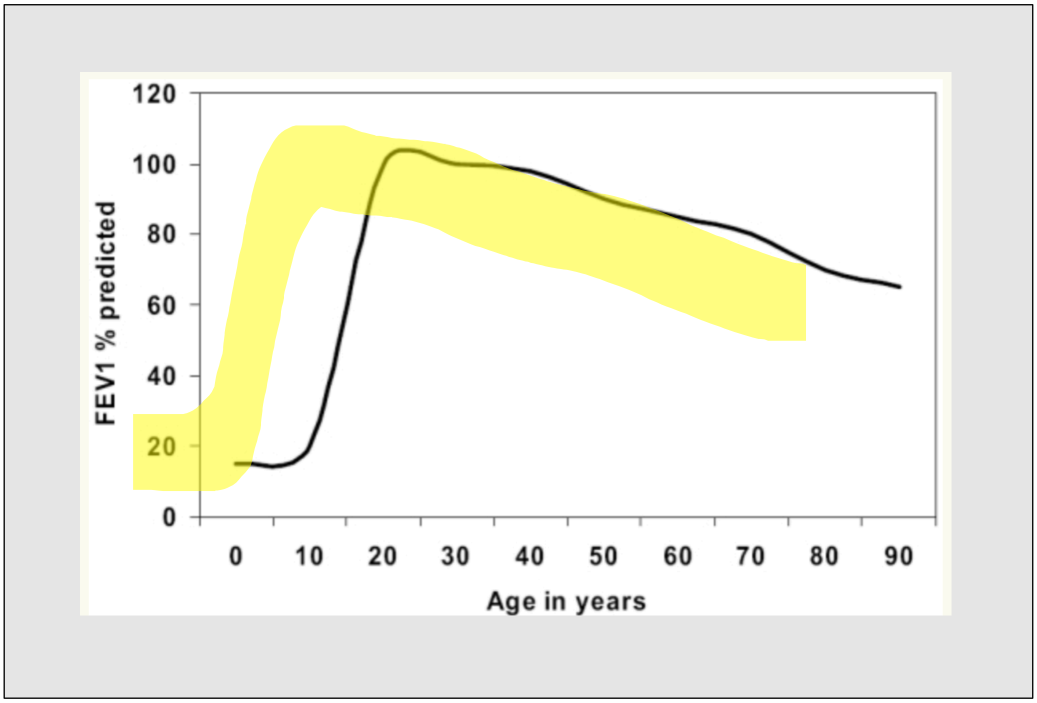
CHAPTER 4

RESPIRATION & INTERMITTENT HYPOXIA

4.1 Respiration Strength for Anti-Aging and a Method for Intermittent Hypoxia

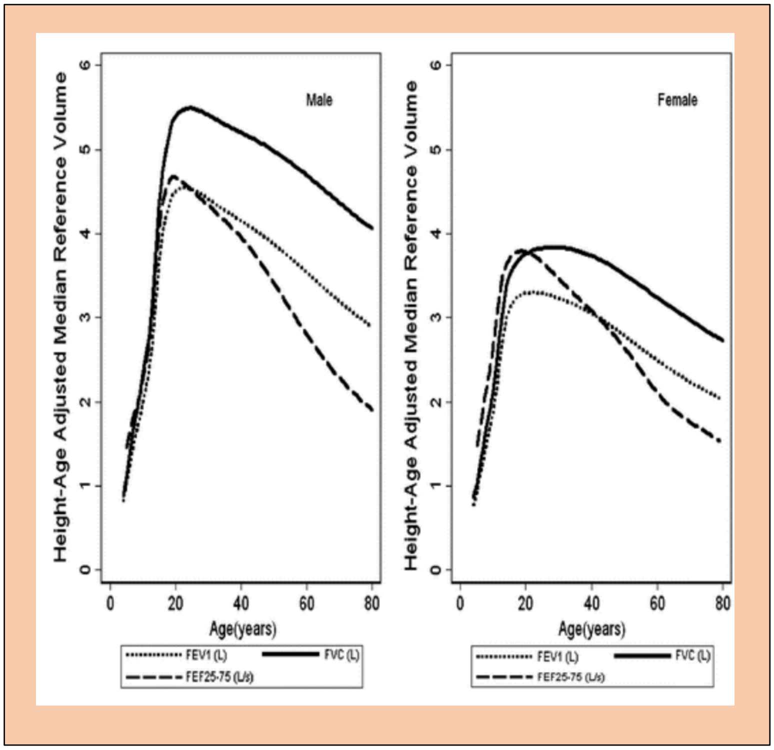
Not only is the rate of sarcopenia, the loss of muscle mass and subsequent strength as we age, at rates as high as 8% per decade after the age of 30 with exponential increases after 60, but respiratory muscles and lung function decline at an alarmingly similar rate, especially if not actively strengthened with specific respiratory/lung strengthening exercises (Shaw et al., 2017; Schermer et al., 2013; et al., 20; Volpi et al., 2004). Combatting the decline in respiratory and lung function is necessary even as early as the second decade of life, during which it may not seem obvious that lung functioning is less than it was 5 years before, but without proper training, the tissue becomes gradually less elastic and powerful (Sharma & Goodwin, 2006). In order to be the most vital with optimal immune function and vibrancy throughout all of the systems of the body, the lungs and respiratory muscles need to be in their strongest and most powerful state (Lowery et al, 2013). Even a 1% decline in this vital organ and the respiratory muscles that are the main operator for cell oxygen absorption and carbon dioxide exit, will contribute to lesser functioning throughout the entire body with cascading effects on every single system in the body (Schermer et al., 2013).

Figure 4



Note: Linear decline in FEV within the second decade of life. Adapted from "Effect of aging on respiratory system physiology and immunology", by Sharma, G., & Goodwin, . (2006). Clinical interventions in aging., 1(3), 253-260. http://doi.org/10.2147/cilia.2006.1.3.253

Figure 5



Note: FEV, FEF, FVC decline with age, peaking just after 20 years of age in both males and females. Adapted from "Reference Ranges for Spirometry Across All Ages: A New Approach", by Stanojevic, S., Wade, A., Stocks, J., Hankinson, J., Coates, A., Pan, H., Rosenthal, M., Corey, M., Lebecque, P., & Cole, T. (2008). American Journal of Respiratory and Critical Care Medicine. 177 (3), 253-260. Http://doi.org/10.1164/RCCL.200708-1248OC

As the reader can see in the above charts, lung function and respiratory muscle function decline at an alarmingly exponential rate over the decades. Because these functions directly correlate to the vitality of every system within our body that make up our functional capacity, functional capacity is lowered dramatically over time (Roman et al., 2016). VO2 max, the maximal amount of oxygen we can consume, is a good representation of the decline in our respiration capacity over time as it declines rapidly with age (Betik & Hepple, 2008).

This is a decline that an individual is able to combat through cardiovascular exercise and respiration/lung exercises (Hagberg, 1987). Beginning at approximately the age of 30 years old, sarcopenia begins to rear its ugly head if it is not combatted with active strengthening of the body (Law et al., 2016). The same is true for lung and respiration mechanics (Jun et al., 2016).

Table 1

Benefits and Definitions Chart of Key Respiratory Health Measures

	Definition/Abbreviation	Recommended Strength Exercises	References for def and strength
Residual Volume	RV: the amount of air in the lungs that cannot be exhaled, keeping alveoli open at all time	Forceful Exhalations to low lung volume; FET, forced expiratory technique, IHT, IHE	Fink, 2007; Lofresse et al., 2020; Yadav et al., 2015
Tidal Volume	TV: the amount of air the moves into and out of the lungs each breath	Exhaling and inhaling to full capacity with breath holds, IHT, IHE	Beutler et al., 2016; Dougherty et al., 208; Karthik et al., 2014; Lee et al., 2017; Vogtel & Michels, 2010
Total Lung Capacity	TLC: the amount of air in lungs at full inhalation	Full inhales with breath holds at the end, IHT, IHE	Ostrowski et al., 2012, Vogtel & Michels, 2010
Forced Expiratory Volume	FEV: the amount of air a person can exhale in a forced breath	Forceful exhales; FET, IHE, IHT, wind instrument playing, blowing up a balloon, resistive breathing, Active Cycle of Breathing Technique (ACBT)	Bourus et al., 2018; Darnley et al, 1999; Karthik et al., 2014; Lewis et al., 2012; Navarrete-Opazo & Mitchell, 2014; Phillips et al., 2004; Seo & Cho, 2018; Tester et al., 2017; Vogtel & Michels, 2010 Yadav et al., 2015
Functional Residual Capacity	FRC: amount of air left in lungs after a normal passive exhale	Active Cycle of Breathing Technique (ACBT); pranayama, IHT, IHE	Dougherty et al., 2018; Lewis et al., 2012
Expiratory Reserve Volume	ERV: the amount of air that can be exhaled passively after a passive exhalation	Forceful exhales to low lung coupes; FET, forced expiratory technique, IHT, IHE, resistive breathing, ACBT	Dougherty et al., 2018; Karthik et al., 2014; Lewis et al., 2012
Inspiratory Reserve Volume	IRV: amount that can be breathed after normal inhalation	pranayama; free diving breath hold, IHT, IHE, resistive breathing	Johansson & Schagaty, 2012; Lee et al., 2017
Vital Capacity	VC: change in volume of lungs from maximum inspiration to maximum exhalation	ACBT, FET, pranayama, wind instrument playing, blowing up balloon, IHT, IHE, free-diving breath hold, resistive breathing	Bourus et al., 2018; Darnley et al, 1999; Johansson & Schagaty, 2012; Karthik et al., 2014; Navarrete-Opazo & Mitchell, 2014; Phillips et al, 2004; Seo & Cho, 2018; Yadav et al., 2015
Forced Vital Capacity	FVC: the amount of air that can be forcibly exhaled from lungs after the deepest inhale	Wind instrument playing, resistive breathing, ACBT, FET, blowing up balloon, singing, IHT, IHE	Bourus et al., 2018; Darnley et al, 1999; Lewis et al., 2012; Navarrete-Opazo & Mitchell, 2014; Phillips et al, 2004; Seo & Cho, 2018; Yadav et al., 2015

Note: Key respiratory health measurements defined and how to strengthen them.

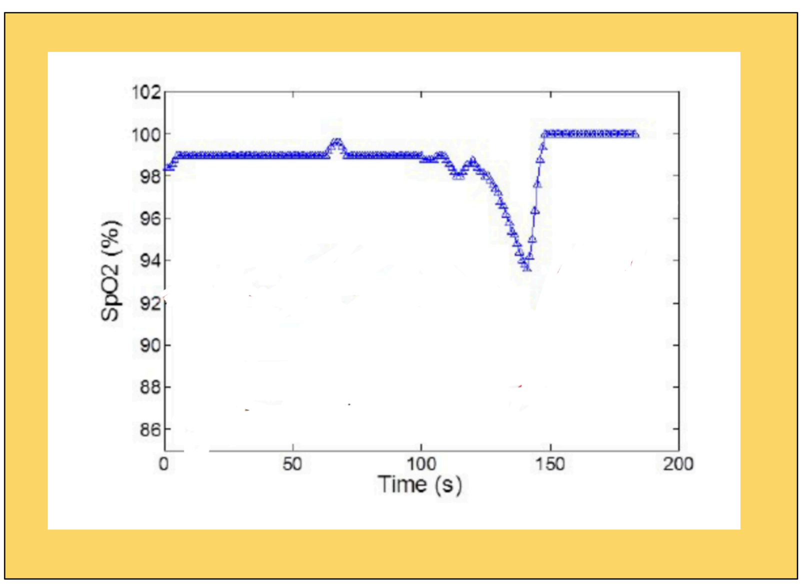
Exhaling to the lowest level air in the lungs is called residual volume, RV, and will be referred to as RV or low lung volume throughout the paper. Working the lungs to RV is a method of strengthening the lungs using techniques such as Forced Expiratory Technique. FET, and Active Cycling of Breathing Technique, ACBT, that has been used by respiratory therapists for decades in order to strengthen the respiration and lung functional capacity of those with lung pathogenesis or a desire to strengthen their non-pathogenic aging lungs (Lewis et al., 2012). Healthy individuals who do not have lung disease are also able to strengthen their lung and respiratory vital capacity through applying components of these techniques, inclusive yogic pranayama, blood to a daily routine (Singh et al, 2012). Evidence shows that while exercise can prevent decline in lung volume and VO2 max, specific breathing exercises are needed to prevent the know decline in FEV (forced expiratory volume) and FRC (functional residual capacity), which are key markers of lung and hence immune health (Hancox, R. J., & Rasmussen, F. (2018). See table 1 for abbreviations and definitions of key lung health measurements and how to strengthen them.

Incorporation of voluntary breathing techniques into a daily workout routine, inclusive of slow breathing at 6 breaths per minute or less, forced exhalations and voluntary apneas or breath holds, have the ability to prevent degradation of all bodily systems by keeping the lungs and respiratory muscles strong that are the gate keepers of functional vital capacity (Russo et al., 2017). Aerobic exercise and strength training in an organized, periodized program, with the appropriate rest integrated into a weekly structure, has been shown to improve total body functional capacity and lower rates of sarcopenia and bone density loss as we age, in addition to preventing chronic disease due to system inflammation (Beavers et al., 2010). Combining a daily a total body exercise routine with a respiratory function routine has the potential to effectively improving age-related decline (anti-aging mechanism) in addition to improving quality of life as a result of the benefits of the central nervous system benefits (anxiety lessening benefits) of daily implementation of a routine that combines a choreographed breathing routine into an exercise routine (Zaccaro et al., 2018). Furthermore, combining a forced exhalation to low lung volume, followed by a short voluntary apnea or breath hold, has been show to significantly increase the recruitment of the lateral abdominal muscles and the deep transversus abdominis, which not only are visually appealing on the beach, but contribute to injury prevention intra-workout and post-workout though effective stabilization of the lumbar spine (Badiuk et al., 2014; Kang et al., 2016; Kim & Lee, 2013; Kim & Kim, 2012; Montes et al., 2015; Shah et al., 2020).

Exhalation to low lung volume, whether combined with a voluntary apnea or not, has been shown to temporarily lower SpO2 levels (Woorons et al., 2007). The extreme version of this is in OSA, in which an individual's sleep is disrupted and they are in a flight or flight, sympathetically driven state, during a time when the body should be recovering from the day parasympathetically (Hakim et al., 2012). Acutely applied moderate intermittent hypoxia (in contrast to the severe experienced in OSA) has been shown to have a cornucopia of health benefits from reduced blood pressure to increased red blood cells through the production of HIF-1 generated factors such as EPO, VEGF and NO (Serebrovska et al., 2016). Incorporation of a voluntary breath routine into an exercise routine, inclusive of forced exhalations, slow breathing and voluntary apneas, has the potential to not only elicit the research-driven benefits created by inducing small doses of intermittent hypoxia, but also is a daily preventative strategy for age related sarcopenia and lung/respiratory decline (Dale et al., 2014; Tregub et al., 2020).

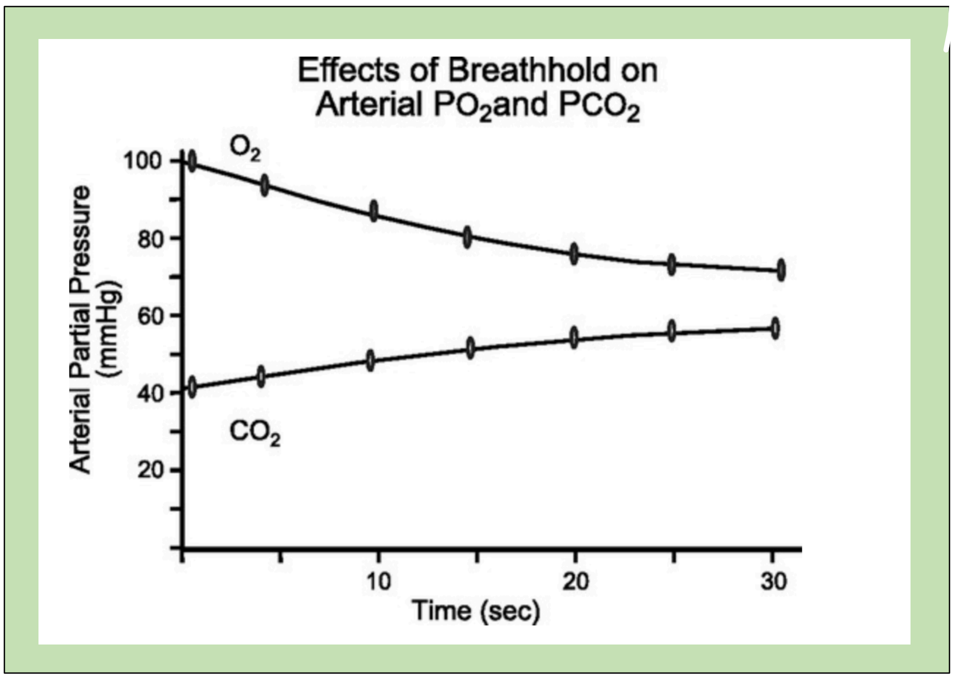
The proposed method of *BIIHT*, breath induced intermittent hypoxic training, is a unique training method that combines all of these elements to keep injury at bay and promote health and vitality. To give the reader a reference point as to what measurements of SaO2s (blood oxygen saturation) can be achieved with a combination of slow exhalations and voluntary apneas on a pulse oximeter (SpO2), the following chart examines the current literature published on SpO2 levels and breath holds techniques, along side the duration of breath holds to reach an effective level to achieve the benefit of IHT of close to 85% SpO2. Falling below 70% SpO2 has been shown to have detrimental effects on the human body, such as that observed in sleep apnea and divers, who hold their breath 10-20 minutes at a time (Serebrovskaya et al., 2016).

Figure 6



Note: SpO2 on breath hold. Adapted from “A Single-Chip CMOS Pulse Oximeter with On-Chip Lock-In Detection.”, by He, D., Morgan, S., Trachanis, D., van Hese, J., Drogoudis, D., Fummi, F., Stefanni, F., Guarnieri, V., & Hayes-Gill, B. (2015). *Sensors* (Basel, Switzerland), 15(7), 17076–17088. https://doi.org/10.3390/s150717076

Figure 7



Note: A comparison of blood CO2 levels and O2 levels in the involuntary apnea of an OSA patient. Adapted from “Using the pathophysiology of obstructive sleep apnea to teach cardiopulmonary integration.”, by Levitzky, M. (2008). *Advances in Physiology Education*, 32(3), 196–202. https://doi.org/10.1152/advan.90137.2008

As seen in figure 7, the blood SpO2 drop at approximately 5 seconds in an OSA patient's breath-hold, which is on an exhalation, is a powerful stimulus for the upregulation of HIF-1 and the subsequent downstream factors such as EPO, VEGF and BDNF (Hertzog et al., 2021; Tregub et al., 2020). It is interesting observe SpO2 levels resulting from the voluntary apneas of a free-diver, which are performed on an inhalation so that the diffusion of oxygen held at "high-lung volume" allows the diver to hold their breath for longer under water in addition to not experiencing as quick a drop in SpO2 levels (Andersson et al., 2002). See figure 10 to reference the longer duration of high SpO2 in a trained breath-hold diver. For the purpose of creating an intermittent hypoxic protocol, that is not as severe or chronic as the sleep disruptive OSA apneic events, a breath hold after a combination of a slow exhale and a forceful exhalation will not only recruit the injury preventative core musculature that protects the low back, but also create quick bursts of low SpO2 levels (Ki et al., 2016; Sforza et al., 2016).

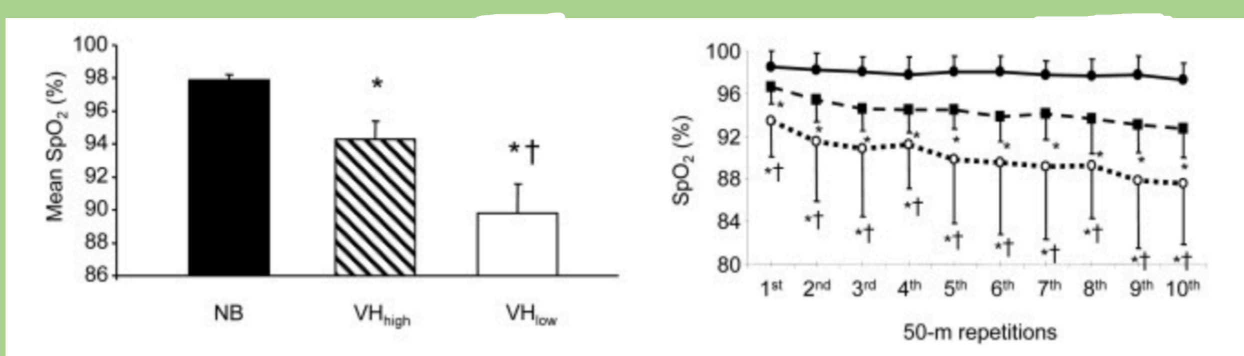
The technique of low lung volume exhalation breath-hold, as is performed in the Woorons research group, shows a very effective level of hypoxemia with low enough SpO2 levels to trigger HIF-1 adaptations, as has been shown in OSA patients, but without the deleterious consequences of the extremely severe and chronic SaO2 that disturbs sleep 8 hours per night (Tregub et al., 2020; Woorons et al., 2017). Observing the drops in SpO2 in the Woorons studies, in which his subjects exhale to low pulmonary volume and implement a breath retention while performing an interval training session, one can see how effective executing a low pulmonary lung volume breath-hold after a maximum exhalation is in creating the intermittent hypoxic cycles necessary to induce the known effective dosing of intermittent hypoxia while exercising using an IHT methodology (Verges et al., 2015; Woorons et al., 2013).

Figure 8

	Baseline	Inspiratory BH	Expiratory BH	Overall *P*	*P* (Within baseline, inspiratory and expiratory breath-holding)
pH	7.40 (0.02)	7.40 (0.03)	7.39 (0.03)	df = 2.20, *P* = 0.437	0.438*, 0.311**, 0.215#
PCO_2 (mmHg)	39.50 (3.10)	42.90 (2.70)	42.10 (2.80)	df = 1.41, *P* < 0.001	<0.001*, 0.001**, 0.062#
PO_2 (mmHg)	94.70 (4.10)	79.10 (9.00)	76.90 (12.10)	df = 1.42, *P* < 0.001	<0.001*, <0.001**, 0.083#
SPO_2 (%)	96.30 (1.90)	95.40 (1.50)	94.50 (2.70)	df = 1.41, *P* < 0.001	0.037*, 0.002**, 0.006#

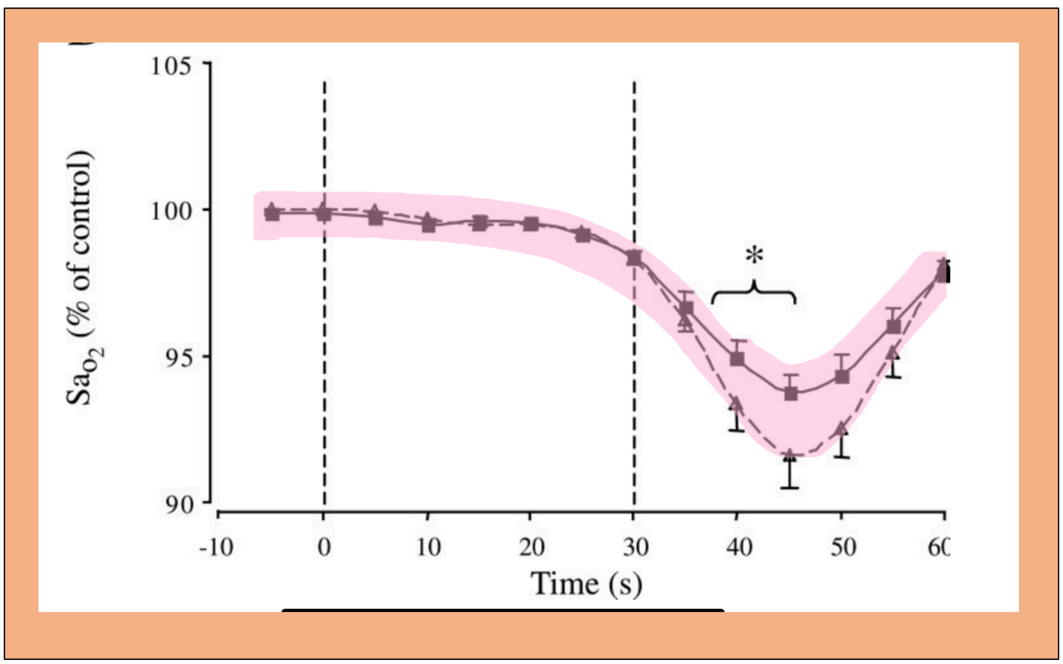
Note: PCO2 and SpO2 levels at breakpoint of breath-hold. “Rhythmic Breath Holding and Its Effect on Arterial Blood Pressure and Its Correlation With Blood Gases.”, by Bhandari, B., Mavai, M., Singh, Y., Mehta, B., & Bhagat, O. (2020). *Acta Medica Iranica*, 57(8), 492–. https://doi.org/10.18502/acta.v57i8.2425

Figure 9



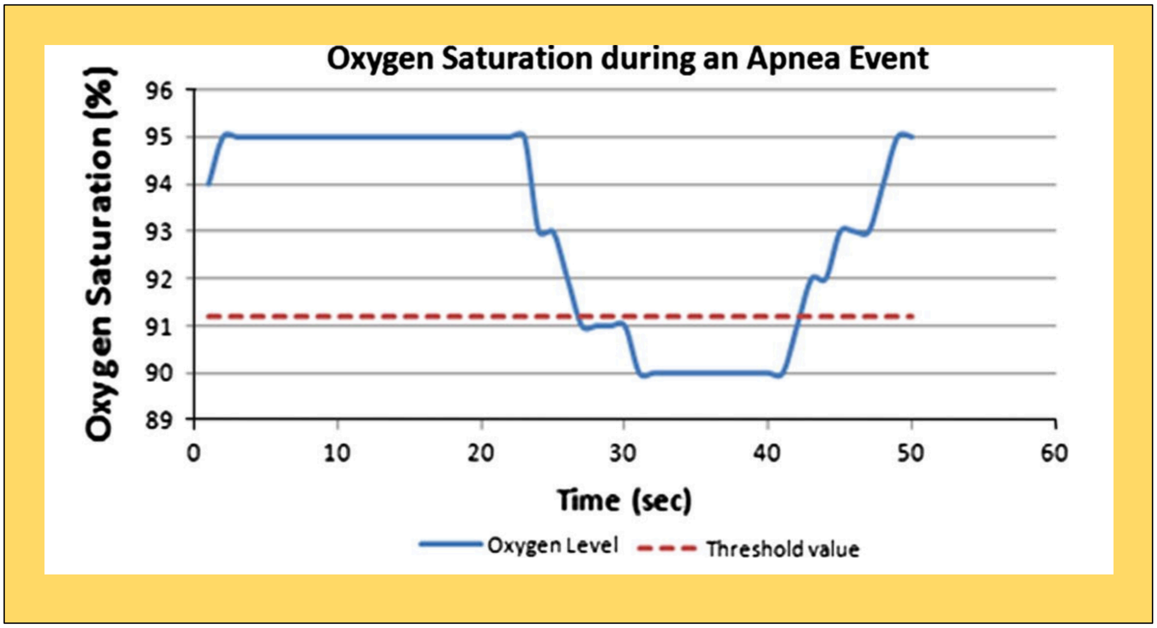
Note: Comparing swimmer's SpO2 levels when breathing normally (NB), high lung volume breath-hold on an inhalation (VHhigh), and breath-hold on an exhalation (VHlow). Adapted from "Swimmers can train in hypoxia at sea level through voluntary hypoventilation.", by Woorons, X., Gamelin, F., Lamberto, C., Pichon, A., & Richalet, J. (2013). *Respiratory Physiology & Neurobiology*, 190, 33–39. https://doi.org/10.1016/j.resp.2013.08.022

Figure 10



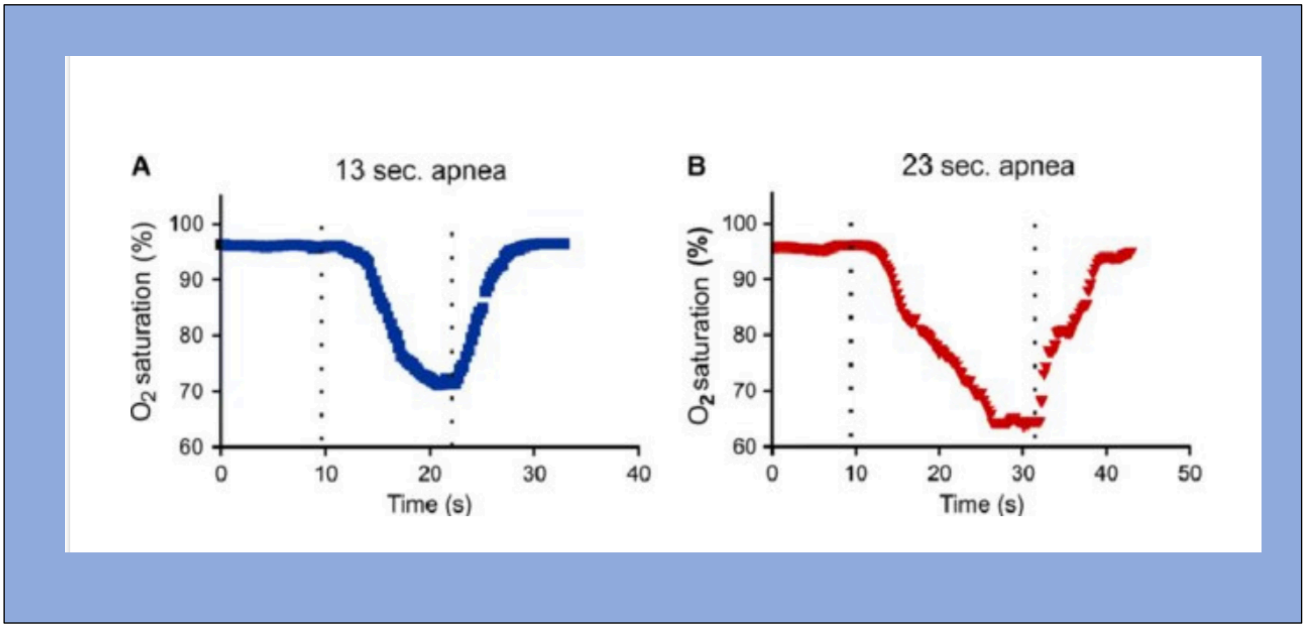
Note: SaO2 levels of a trained breath-hold diver during a 60 second face-immersed breath-hold. Adapted from "Diving response and arterial oxygen saturation during apnea and exercise in breath-hold divers.", by Andersson, J., Liner, M., Runow, E., & Schagatay, E. (2002). *Journal of Applied Physiology*, 93(3), 882–886. https://doi.org/10.1152/japplphysiol.00863.2001

Figure 11



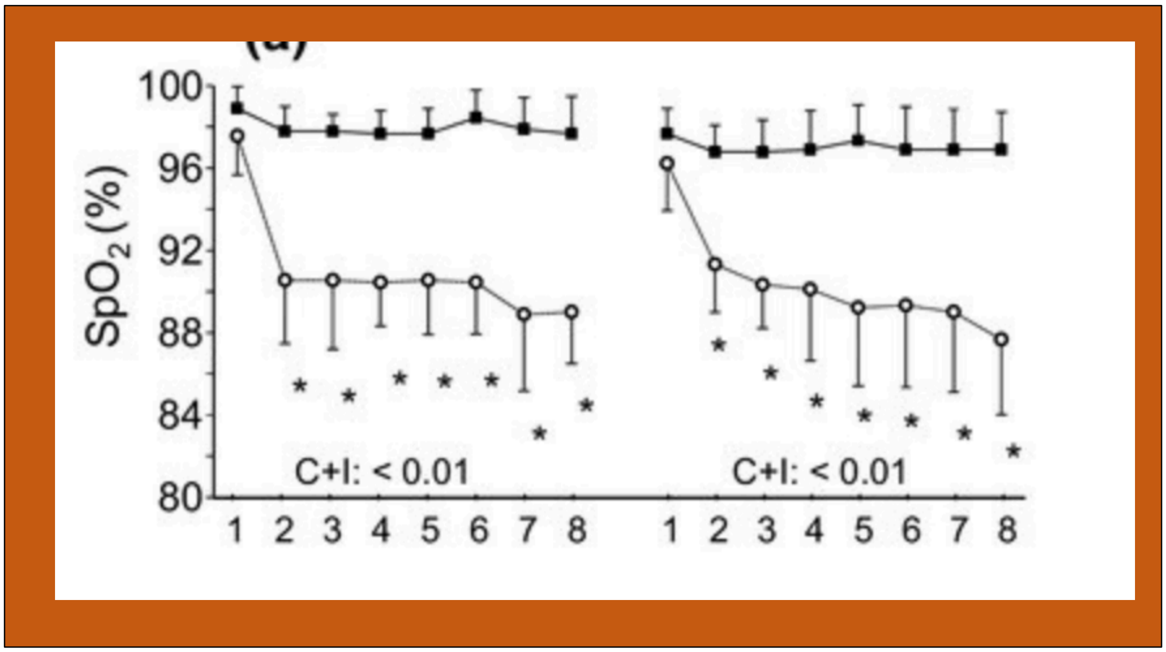
Note: Typical SpO2 drop in an apneic event during one 30 second cycle in OSA patient. Adapted from "Classifying obstructive sleep apnea using smartphones.", by Al-Mardini, M., Aloul, F., Sagahyroon, A., & Al-Husseini, L. (2014). *Journal of Biomedical Informatics*, 52, 251–259. https://doi.org/10.1016/j.jbi.2014.07.004

Figure 12



Note: Severe fall in SpO2 in an OSA patient. Adapted from "Atrial electrophysiological and molecular remodelling induced by obstructive sleep apnoea.", by Channaveer ppa, D., Lux, J., Wormwood, K., Heintz, T., McLerie, M., Treat, J., King, H., Alnasser, D., Goodrow, R., Ballard, G., Decker, R., Darie, C., & Panama, B. (2017). *Journal of Cellular and Molecular Medicine*, 21(9), 2223–2235. https://doi.org/10.1111/jcmm.13145

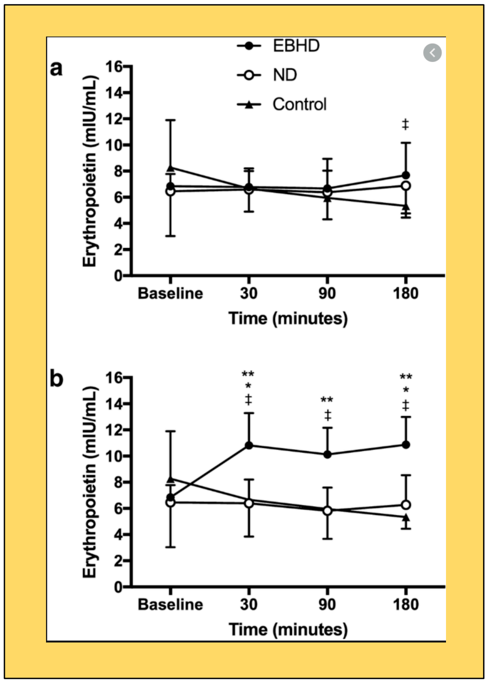
Figure 13



Note: Minimum SpO2 levels when performing sprints with breath hold at low lung volume. Adapted from "Acute effects of repeated cycling sprints in hypoxia induced by voluntary hypoventilation.", by Woorons, X., Mucci, P., Aucouturier, J., Anthierens, A., & Millet, G. (2017). *European Journal of Applied Physiology*, 117(12), 2433–2443. https://doi.org/10.1007/s00421-017-3729-3

In order to prevent maladaptation, utilization of breathing technique combining forceful exhalations to low lung volume and a breath-hold duration necessary to achieve an effective 80-90% blood oxygen level is a method of creating a stimulus without the accompanying deleterious effects. Because this level has been shown to be effective, the minimum effective dose shall be emphasized (Schega et al., 2013). Applying a minimum effective dose whether in exercise, diet, or breathing falls in line with the beneficial effects of hormesis (Mattson et al., 2008). Applying more than a minimum effective dose has the ability to push the organism into distress and the exhaustion phase of Selye's GAS, which minimizes a person's potential for positive adaption (Selye, 1950). Many factors, inclusive of EPO, have been shown to rise in levels in response to a breath-hold as a result of the apnea-induced HIF-1 (Elia et al, 2019). Factors such as EPO are not only protective to organs such as the brain, heart and kidney, but also have a performance enhancing effect (Nguyen et al., 2014; Trina et al., 2020) . More research is needed in the area of application of low lung volume voluntary apneas during an IHT program to further explore the proper dosing for the most beneficial metabolic, bioenergetic, musculoskeletal, central nervous system, and cardiovascular effect.

Figure 14

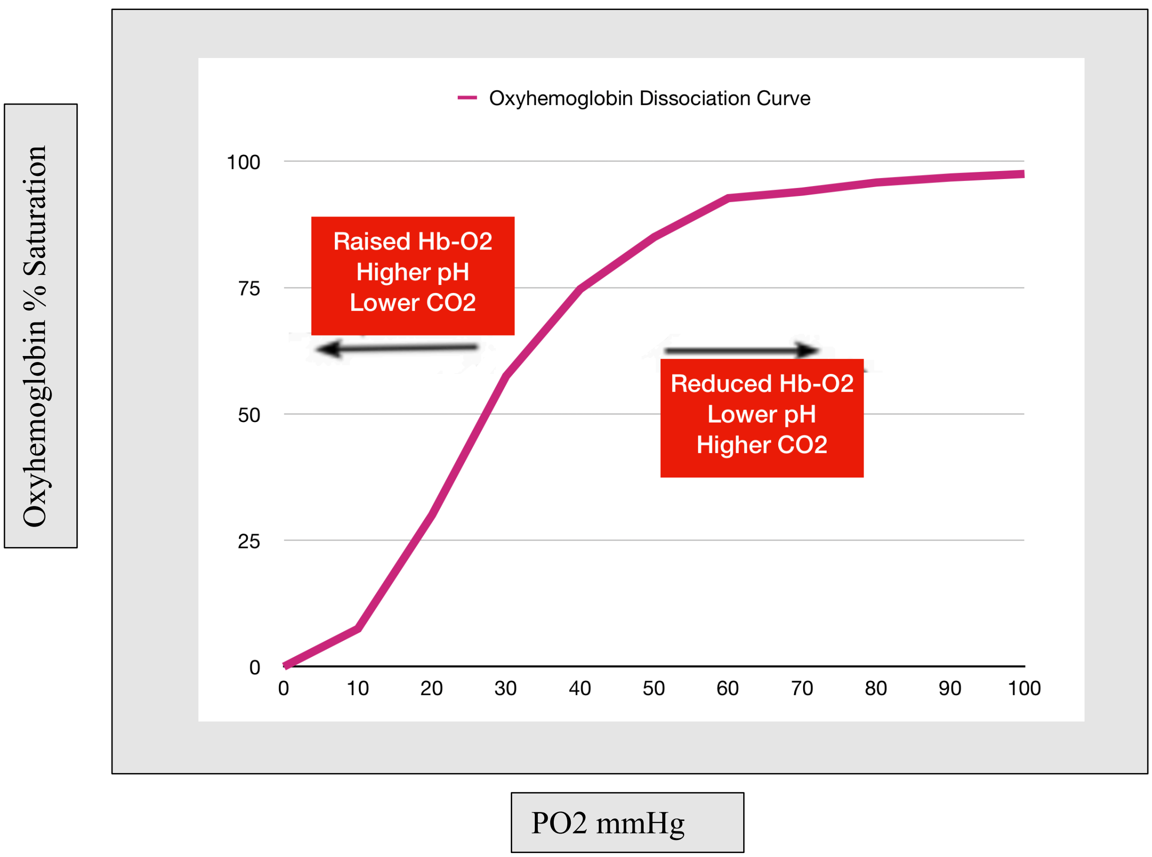


Note: Static breath holds vs dynamic cyclic breath holds vs control group. Adapted from "Erythropoietic responses to a series of repeated maximal dynamic and static apneas in elite and non-breath-hold divers.", by Elia, A., Barlow, M., Deighton, K., Wilson, O., & O'Hara, J. (2019). European Journal of Applied Physiology, 119(11), 2557–2565. https://doi.org/10.1007/s00421-019-04235-1

4.2 Bohr Model, The Oxyhemoglobin Dissociation Curve, and Voluntary Apnea

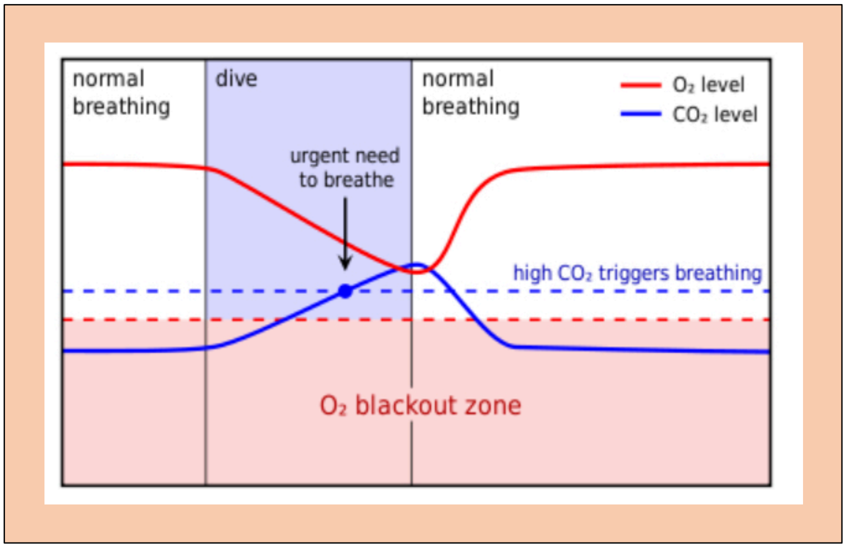
The oxyhemoglobin dissociation curve demonstrates The Bohr Effect. When the breath is held or the body is exposed to hypoxia training, the SaO2 lowers, CO2 levels rise, and the hemoglobin affinity for oxygen decreases as it is released into the body's tissues (Dickson, 1995). The Bohr Effect states that as the blood oxygen saturation decreases, hemoglobin's affinity for oxygen decreases as the CO2 levels and blood pH levels rise, resulting in the hemoglobin unloading oxygen molecules into the tissues of the body such as the brain and muscle (Benner et al., 2020). There are periods of greater oxygen perfusion in the brain, muscle tissue and other organs during both breath retention and intermittent hypoxic exposure and training due to the concept of the Bohr Effect (Terasawa et al., 2010). Intermittent Hypoxic Training, IHT, takes advantage of this effect as the muscles are more greatly oxygenated while training in hypoxia (Mairbäurl, 2013).

Figure 15



Note: Oxyhemoglobin Dissociation Curve.

Figure 16



Note: Urgent need to breathe as CO2 levels rise, O2 lowers and hemoglobin loses affinity for oxygen. Adapted from "What are apnea tables?", by Irion, D. (2018). Retrieved from: https://www.caperadd.com/news/what-are-apnea-tables/

4.3 Breathing Intra-Workout

Voluntarily choreographing one's breath in tandem with movement has existed for millennia (Sengupta, 2012). Pranayama, a yogic form of meditative breathing, has been shown to not only improve cognition and lung capacity, but also cardiovascular functioning such as HRV and blood pressure (Campanelli et al., 2020). Many forms of pranayama have also been shown to strengthen the abdominals through a practice of drawing the belly button in, the abdominal draw in maneuver, while exhaling such as Zen Tanden (Zaccaro et al., 2018). In addition to the muscular, central nervous, pulmonary and cardiovascular strength, certain methods of yoga that include breath retention, such as nisshesha rechaka, have proven to provide doses of intermittent hypoxia throughout the practice (Malshe, 2015). Although not a lot of research has been focused in this area, there are a handful of scientists who are very interested in the physiological adaptations of performing breath-holds, both during exercise and passively. The hypoxic state in free-divers have been studied for decades to observe their drops in O2 and pH, and subsequent rises in CO2 and HIF-1 sending a cascade of downstream effects to organ-protective and performance boosting EPO and VEGF with the coinciding rise in red blood cells and oxygen carrying capacity (Mulder & Schagatay, 2021). The long breath-holds of free divers can be detrimental to blood pressure and oxygen delivery to brain, but shorter breath-holds that lower SaO2 to a level that promotes adaption of 80-90% SaO2, have been shown low risk and eliciting positive adaptations (Serebrovskaya & Xi, 2012; Steinberg & Doppelmayr, 2019).

Many studies have highlighted the benefit of performing a breathing rate of 6 breath per minute as the most therapeutic in terms of improving HRV, blood pressure, and heartrate (Russo et al., 2017). Pilates breathing, typically performed at a rate close to 60 bpm, has been shown to improve HRV in addition to strengthening the core musculature effectively to prevent injury and reduce low back pain (Kuppusamy et al., 2020; Lim & Yoon, 2017). Resistive exhaling or inhaling with either a breathing device, musical instrument or pursed lips or “shh” breathing has been shown to strengthen the core in a passive seated position in addition to strengthening the core muscles with higher EMG activation levels in contrast to an involuntary breathing control (Ishida et al., 2017; Shah et al., 2021).

Many breathing methods that are employed in conjunction with a workout are popular today and combine breath choreography into the workout routine. The Wim Hof method is one that instructs a combination of hyperventilation, forced inhales, and breath-holds while both passively and actively performing exercise, all the while exposing oneself to the cold

(Muzic et al., 2018). This method has been shown to be able to enhance immune function in the few studies that were performed through suppression of pro-inflammatory cytokines (Kox et al., 2014). The strong history of voluntary breath work sets the stage for a bright future of continuing on this path with a deeper focus on how breath holds can positively affect a person's physiology alongside a workout without causing maladaptation.

Slow breathing has the ability to reverse the action of some of the mitochondrial metabolic consequences such as ROS, reactive oxygen species, and RNS, reactive nitrogen species, that are consequences of pushing the system too hard, which can be a byproduct of too much exercise, too much stress, or too much hypoxia (Di Meo et al., 2016; Russo et al., 2017). The current science confirming the power of the breath to strengthen the anti-oxidant pathways is a feature that intuitively was felt by the practitioners of early pranayama thousands of years ago in India (Saoji et al., 2019). Combining slow breathing with a daily exercise routine, including intermittent hypoxia, can strengthen the anti-oxidant pathways via upregulation of the parasympathetic nervous system, fortifying an army of anti-oxidants within the system that can help to combat the ROS or RNS that result from too much exercise, stress or excessive hypoxia (Di Meo et al., 2016; Sengupta et al., 2012).

Heartrate variability, HRV, which is the relationship between the parasympathetic and the sympathetic nervous system, is improved with higher scores in most of the literature that studies slow breathing rates of 6 breaths per minute (Li et al., 2018; Zaccaro et al., 2018). Improvements in HRV scores correlate with better immune function, cardiovascular health, cognition, recovery, and longevity (Cooper et al., 2015; Ernst, 2017; Young & Benton, 2018). Furthermore, hormetic, small doses of the aforementioned stressors of exercise, mental stress and hypoxia all help to strengthen the anti-oxidant pathway by spiking small doses of reactive oxygen and nitrogen species, which is an amount that the body can adapt to and strengthens anti-oxidant pathways through the surge in anti-oxidant production in response to these small doses of inflammatory ROS and RNS (Cai et al., 2021; Hertzog et al., 2021). Therefore, combining slow breathing and intermittent hormetic doses of *eustress* (small doses of exercise, breath strength routines including breath-holds, and intermittent hypoxia) strengthens mitochondrial metabolic health, supporting a vital organism with a high functional capacity (Aschbacher et al., 2013; Picard & McEwen, 2018).

4.4 Components of Respiration Strength Training

While performing small doses of aerobic/anaerobic exercise, strength training, intermittent hypoxia, and breathing exercises all have been shown to be highly beneficial when performed at acute doses with an adequate amount of rest in between applications, execution of any of these activities to a high degree of intensity, duration, and frequency can have the opposite effect (Goldstein, 2010). Selye's GAS model comes into play again in terms of a breath-routine for strengthening the lungs, abdominals, respiratory muscles, and mind, all of which are affected by the natural process of aging (Jung et al., 2021). An "anti-aging" breath routine would incorporate acute doses of low intensity breath retention, slow breathing at 6 breaths/minute and forced exhalations to strengthen areas such as tidal volume (TV), forced vital capacity (FVC), forced expiratory volume (FEV), inspiratory reserve volume (IRV), expiratory reserve volume (ERV), functional residual capacity (FRC), and the strength and elasticity of the lungs and supporting abdominal respiration muscle system (Lowery et al., 2013; Sharma & Goodwin, 2006).

An extreme dose of breath training has the potential to be hazardous to one's health, such as the 11 minute breath-holds that are performed by elite static dry-land apneists and the long breath holds of a free diver (Steinberg & Dopplmayr, 2019). While the mammalian diving reflex is an in-born system that aids in a human's survival with these long breath holds that bring the SpO2 down to as low as 50% by vasoconstriction of the peripheral tissues in order to keep oxygen high to the brain in addition to slowing of the heart, bradycardia, for survival of the organism while retaining the breath for several minutes, this extreme version of retaining one's breath has been shown to raise blood pressure, create an abnormal shift in transpulmonary pressure of the alveolar epithelium leading to alveolar hemorrhage, and possible death if practicing breath-holding without a partner when unconsciousness arises underwater (Ostrowski et al., 2012). Although these are the worst possible symptoms that an extreme breath-hold can produce, they are worthy of note and one must question whether or not the elite apneists who never experience any of these conditions have a genetic predisposition to perform at an elite level, as has been shown across many elite sports (Guth & Roth, 2013).

Interestingly, while the aforementioned negative consequences as a result of an extreme breath-hold exist when a human pushes into that extreme exhaustion phase of GAS with the breath holding activity, some positive physiological adaptations have been shown in elite breath holders such as improved residual volume (RV), total lung capacity (TLC), improved forced expiratory volume (FEV), increased threshold of chemoreceptor sensitivity and improved strength in the respiration muscles that support these components of excellent lung and respiratory health (Bain et al., 2018; Diniz et al., 2014; Walterspacher et al., 2011). Historically, it has been suggested that working TLC and RV past normal values could result in lung trauma such as rupture, but this has been discounted as the method of glossopharyngeal breathing in the 1950s as performed with post-poliomyelitic patients resulted in positive outcomes (Bhandari et al., 2019; Mijacika, & Dujic, 2016).

Again, working the lungs and respiratory muscles is similar to working the quadriceps in a deep squat or the biceps in a biceps curl. Short, acute doses with adequate rest in between assists in keeping the organism in the positive adaptation phase of Selye's GAS model without pushing the organism into the exhaustion phase. Wind instrument players and opera singers have also been shown to have improved pulmonary markers such as TLC, RV, FEV, core functioning and immune health with implementation of breath training, inclusive of elongated exhalations, forced exhalation, breath-holds and resisted inhalations (Bouros et al., 2017; Ksinopoulou et al., 2016). Many of the lung measurements in table 1 have been linked to increased CRP, C-reactive protein, total body inflammation, lung inflammation and an overall lowering in the immune system when they are not optimally strong and functioning to keep the pulmonary system functioning as it should (Fogarty et al., 2007; Glaser et al., 2012; Lofrese et al., 2020) Most of these measurements decline with age and should be actively strengthened in order to avoid rapid decline (Thomas et al., 2019)

Forced Expiratory Technique (FET) has been used as a method to assist in strengthening the lungs and respiration muscles of those afflicted with lung disorders to help in clearing mucous from the lungs, an action that reduces debris and mucous, which can be the cause of subsequent chronic lung inflammation and respiratory infections (Fink et al., 2007). The ability to forcefully exhale as we age declines rapidly, in line with other areas of lung function such as TLC, RV, FEV, FRC, corresponding with the muscles structures that support healthy pulmonary function through the process of sarcopenia (Jung et al., 2021;

Lowery et al., 2013). Even though FET is mostly limited to a pathological patient population with lung disorders, this does not mean that FET cannot be implemented in normal healthy populations for the same positive outcomes such as improvements in all of the aforementioned areas that tend to slowly decline with age. Incorporation of deep, slow and forceful breath manipulations could be a key component to a daily practice of anti-aging (Zaccaro et al., 2018).

The breath-hold practice of healthy elite divers that improves RV and TLC is inclusive of forceful exhalations down to below RV in order to then take in more oxygen with an inhale, increasing TLC, through the greater difference in pressure (Bain et al., 2018). Improvements in RV and TLC directly correlate with health and longevity. As demonstrated in the above charts, RV and TLC values directly correlate with lung health, prevention of cognitive decline and promote a longer life (Dodd, 2015; Yoon et al., 2015). Combining the lung strengthening benefits of singing, wind instrument playing, or free-diving with the aforementioned athletic and hypoxic benefits of the Xavier Woorons method of working to low-lung volume exhalation could be an effective combination of techniques to elicit performance enhancing and immune enhancing effects (Serebrovska et al., 2016). Woorons and his colleagues have performed multiple studies over the past 20 years that show the athletic benefits of performing breath retention to create hypoxia within the system intra-workout, inclusive of improved muscle buffering capacity, increased motor unit recruitment, increase glycolytic metabolism, increased type ii muscle fiber recruitment and improved speed (Jung et al., 2021; Woorons et al., 2017).

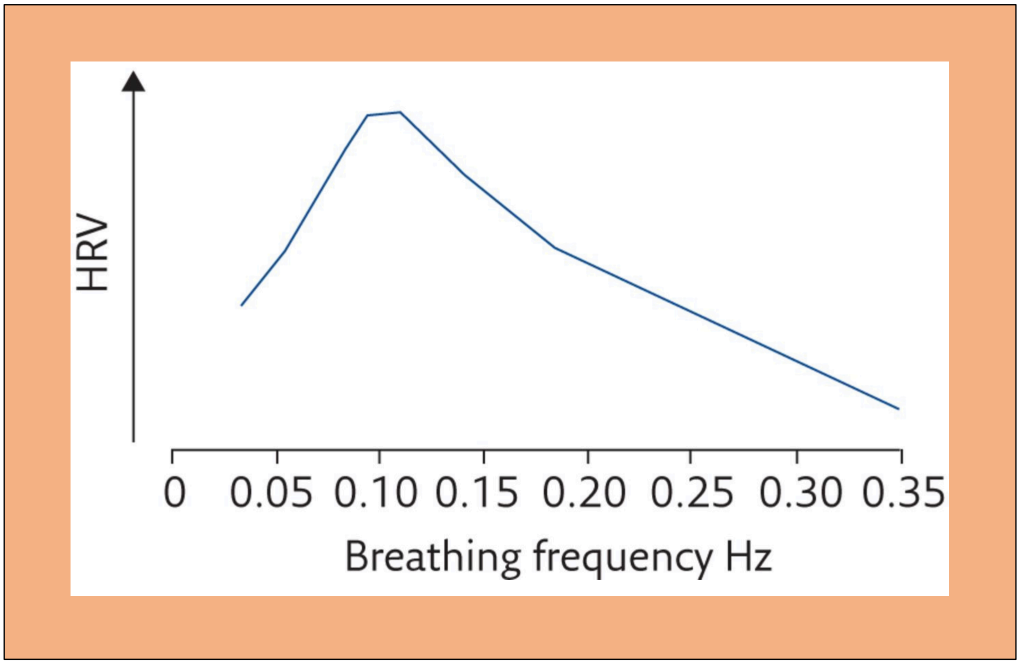
What Woorons has not measured in his research is the coinciding improvements in lung functions and the respiratory and abdominal muscles that support the technique that he calls hypoventilation training. This missing link must be further explored and there are several proposals for scientific research in the appendices section. A plethora of research has shown that performing exercises with forceful or resisted exhalations increases the recruitment of key abdominal muscles such as the internal oblique, external oblique and transversus abdominis, all of which are key muscles in injury prevention via their ability to stabilize the lumbar vertebrae and lumbo-pelvic hip complex (Ishida et al., 2017; Ito et al., 2016; Montes et al., 2016; Sugimoto et al., 2018). Performing maximum exhalations was shown in a study to be more effective at recruitment and strengthening of key abdominal muscles such as internal and external oblique in comparison to a group who performed the same exercises, such as plank and curl up, breathing normally (Kim & Park, 2018). Furthermore, it has been shown that a forceful exhalation to residual volume (RV) increases activity of the internal oblique and external oblique musculature more so than the rectus abdominis when performing a seated forced exhalation, uncoupled with exercise (Shah et al., 2021).

If forceful exhalation has the ability to increase the activation and therefore strength of the obliques, especially the internal oblique, in exercises where the rectus abdominus has the ability to dominate, this could have outstanding clinical implications. The dominance of the rectus abominis is a muscle trait that those with diastasis recti, a larger than normal gap between the muscles of the rectus abominis and subsequent stretching of the linea alba connective tissue, and abdominal hernia complications can suffer from (Jensen et al., 2019). Additionally, pre-natal and post-natal training, inclusive of exercises that attempt to “upregulate” core muscles such as internal oblique, pelvic floor, multifidi and diaphragm and “downregulate” the rectus abdominis, could benefit from breath training to induce proper core functioning and prevention of diastasis recti (Hinman et al., 2015; Rajalakshmi & Senthil

Kumar, 2012). Because the use of forceful exhalations are not only shown to improve lung function and strengthening of the key abdominal muscles that aid in prevention of injury and hernia, a forceful exhalation is suggested for use as part of a workout routine that optimizes health and longevity.

HRV, heart rate variability, a key measurement in cardiovascular health that represents the relationship of the parasympathetic and sympathetic nervous system, has been shown in countless studies over the past several decades to be improved with the use of breathing training, especially long exhalations of 6 breaths per minute (Russo et al., 2017). Working the lungs to full TLC and RV requires an extended amount of time than that which would be experienced if breathing normally (Tzelepis et al., 1994). While a forceful exhalation that works to “squeeze” the air out at a high rate will not be as slow and focused as a long, drawn out and less forceful breath, it still constitutes slowed down and focused breathing that can be in support of a high parasympathetic tone, which is indicative of a high HRV (Sengupta et al., 2012). A combination of forced exhalations, slow relaxed breathing at a rate of no more than 6 breaths per minute and short breath retentions that condition not only the TLC and RV, but also the chemoreceptor sensitivity (the threshold at which increasing CO2 levels in the blood send signals to take an inhalation) can be optimized by combining these elements with a workout routine for optimal functional vitality (Clark & Godfrey, 1969, Parkes, 2013). The connection between HRV, breath and intermittent hypoxia will be further elucidated on in the following areas of cardiovascular health, obesity, cognitive decline and athleticism.

Figure 17



Note: HRV peaks at 0.10 Hz, which is 6 breaths per minute or 10 seconds per breath. Adapted from "The physiological effects of slow breathing in the healthy human", by Russo, M., Santarelli, D., O'Rourke, Dean., *Breathe (Sheffield, England)*, *13*(4), 298–309. https://doi.org/10.1183/20734735.009817

In terms of the importance of regulating the tempo of the breath, there is reason to use a slow breath at 6 breaths/min vs a fast shallow breath to induce intermittent hypoxia. Fast breathing could induce hyperventilation, which causes hypocapnia and respiratory alkalosis, in which the levels of blood CO2 become too low, raising the blood pH, overproducing HCO3- and causing dizziness and nausea (Folgering, 1999). The Bohr Effect describes the relationship between O2 and CO2. As CO2 levels rise in the body and the blood pH lowers, hemoglobin's affinity for oxygen is reduced and the oxygen molecules disassociate from the hemoglobin in order to supply the tissues in the body with much needed oxygen (Brenner et al., 2020). Therefore, when CO_2 levels rise in the body due to a slow breath and voluntary apnea, O_2 is then disassociated from the hemoglobin molecule and sent to the tissues that most need the O_2. During IHT, the muscle tissue has a high demand for oxygen as the perfusion to the muscle can increase up to 76 fold its resting perfusion during exercise (Parks et al., 1983). Therefore, performing breathing exercises to induce intermittent hypoxia could be a unique way of utilizing the Bohr Effect to create an even more effective IHT session. Performing a workout that combines the benefits of lung health, respiratory health, aerobic/anaerobic health, muscle health and core health could aid in optimal vital daily functional capacity, reduction in injury rates, an improved immune system and a longer life, based on the research of voluntary breath training in conjunction with both exercise and intermittent hypoxia (Asimakos et al., 2018).

In addition, there is much debate in the respiratory therapy community on the benefits of *therapeutic hypercapnia* (Kavanagh, 2005; Tao et al., 2013). Therapeutic hypercapnia is a form of respiratory therapy that preconditions the individual to hypercapnic events by exposing subjects to higher levels of CO_2, which elevates the blood levels of CO_2, lowers the blood pH temporarily, and can be implemented using intermittent hypoxia (Yang et al., 2019). Interestingly, a study looked at the effects of hypercapnia with hypoxic exposure and compared this group to a no-hypercapnia group with hypoxic exposure on the effects of HIF-1 levels in the hippocampus (Tregub et al., 2020). They found that the combination of hypercapnia and hypoxia was more effective than hypoxia on its own in upregulating HIF-1, which is the main transcription factor that triggers the beneficial effects of intermittent hypoxia (Qiao et al., 2018). Could it be that exhaling to a breath-hold on low lung volume can assist in increasing levels of HIF-1 in the central and peripheral tissues, induced by the acute doses of high CO2 induced by the hypercapnic respiratory acidosis? Could the combined stimuli of intermittent, hormetic doses of respiratory acidosis using a breath method in conjunction with an external stimulus of IHE or IHT, such as a hypoxic chamber, prove to be more effective at elevating levels of HIF-1 levels than a hypoxic chamber stimulus alone? A proposed method of breath-induced intermittent hypoxic training (*BIIHT*) has the ability to condition all of these areas optimally, especially if supported by future research. Implementing hypoxia through a combination of forced exhalations, slow exhalations, and voluntary apneas not only lowers blood pH and raises CO2 temporarily, but it also strengthens the respiratory muscles, including the injury preventing abdominals, and retains lung vital capacity measurements (Ma et al., 2017). This proposed method, alongside suggested exercise samples, is discussed more in detail in the future perspectives section at the end of the paper if it piques the reader's interest.

4.5 Hypothesis & Proposed Mechanism

Experimental Hypothesis: If intermittent hypoxia can be induced with a combination of slow exhales, forceful exhalations, breath holds (voluntary apneas) strategically throughout a workout to not only employ the proven health and performance benefits of IHT, but also strengthen respiration and core musculature for ant-aging and injury prevention, the garnered convenience and efficacy of intra-workout voluntary breathing mechanisms could cause a paradigm shift in the definition and execution of a truly efficient and effective workout. This hypothesis will be analyzed thoroughly throughout the following examination of the effects of voluntary breathing and intermittent hypoxia on cognition, performance, and chronic disease. The proposed methodology is breath-induced intermittent hypoxic training, *BIIHT*, which incorporates elements of forceful exhalation to low lung volume, breath holds (voluntary apneas) and a slow breathing rate of 6 breaths per minute in order to maximize lung strength, respiratory strength, abdominal strength, and the benefits garnered from temporarily lowering the SaO2 levels. The breath holds at low lung volume are strategically set throughout the workout to mimic some of the shorter, more acute doses of IH protocols, such as those that are seen in the labs for SCI, spinal cord injury, for respiratory therapy, but not so severe that they would mimic the apneas as seen in OSA (Naverrete & Mitchell, 2014). This hypothesis will be explored further throughout the following sections dissecting the connection between the benefits of controlled breathing, breath holds and intermittent hypoxia induced from a variety of methods inclusive of voluntary apneas, altitude and hypoxic chambers.

In the future perspectives section at the conclusion of the paper, there are proposed examples of a hypothetical *BIIHT* program corresponding with images demonstrating the breath routines in conjunction with correspond suggested breath choreography or "breath-ography" to maximize abdominal recruitment, upregulate the parasympathetic nervous system and strategically lower SpO2 levels in a cyclical way. *BIIHT* tempo, intensity and duration is research driven and designed to achieve the greatest possible response in HIF-1 with the breathing in order to theoretically stimulate EPO, BDNF, VEGF, NO and the other beneficial downstream effects from the production of HIF-1 (Dale et al., 2014).

Table 2

% FiO2	Altitude Meters Above Sea Level	Altitude Feet Above Sea Level
21%	0	0
20.1%	304	1000
19.4%	609	2000
18.6%	914	3000
17.9%	1219	4000
17.3%	1524	5000
16.6%	1828	6000
16%	2133	7000
15.4%	2438	8000
14.8%	2743	9000
14.3%	3048	10000
13.7%	3352	11000
13.2%	3657	12000
12.7%	3962	13000
12.3%	4267	14000
11.8%	4572	15000
11.4%	4876	16000
11%	5181	17000
10.5%	5486	18000
10.1%	5791	19000
9.7%	6096	20000

Note: FiO2 vs. Altitude Chart . Adapted from "Clinical recommendations for high altitude exposure of individuals with pre-existing cardiovascular conditions.", by Parati, G., Agostoni, P., Basnyat, B., Bilo, G., Brugger, H., Coca, A., Festi, L., Giardini, G., Lironcurti, A., Luks, A., Maggiorini, M., Modesti, P., Swenson, E., Williams, B., Bärtsch, P., & Torlasco, C. (2018)., European Heart Journal 39(17), 1546–1554. https://doi.org/10.1093/eurheartj/ehx720; "Hypoxico Altitude to Oxygen Chart", (2020), Retrieved from: https://hypoxico.com/altitude-to-oxygen-chart/

CHAPTER 5

THE ATHLETE

5.1 The Athlete, Altitude and IHT

Increased speed and endurance, through mechanisms of increased ability to buffer intra-cellular acidic environment, both elite and sub-elite athletes have been integrating various forms of hypoxic exposure to improve athleticism for decades (Khodaee et al., 2016). The surge in the interest of altitude hypoxic training peaked after the Mexico City 1968 Olympics, during which athletes experienced both advantages and disadvantages in their performance (Serebrovska et al., 2016). Because altitude training methodologies inclusive of living high, training low, LH-TL, in which the athletes lives and sleep altitude, but train at sea level in order to not experience the potential performance degrading elements that hypoxia can impose, and living low training high, LL-TH, in which the athlete lives and sleeps at sea level and trains at altitude to benefit from exposing the body to hypoxia while performing at high intensity, will be touched on in the following section to provide the reader with an understanding of intermittent hypoxic and altitude training, but will not be the main focus in subsequent sections, as these methodologies have been examined for several decades with thousands of studies and research articles devoted to this topic (Strzala et al., 2011). Levine & Gunderson (1997) were able to show conclusively that the LH-TL model was superior to the same training program at sea level in terms of increased erythrocyte production, which stems from HIF-1 signaling EPO in the kidney to stimulate red blood cell (erythrocyte) production in the bone marrow, which enables the athlete to have greater oxygen carrying capacity through an increased hematocrit, higher hemoglobin count and more oxygen utilization to power the muscles of the athlete (Levine & Gunderson, 1997). Scientists Levine and Stray-Gunderson have collaborated on many studies regarding athletic hypoxic training and are the inventors of the live-high-train low (LH-TL) model in the early and mid-1990s (Stray-Gunderson & Levine, 2008). Their early studies, in which the athletes lived at about 2500m above sea level and trained at sea level, showed consistent increases in EPO, erythropoietin, and subsequent increases in hematocrit, hemoglobin, oxygen carrying capacity and the coinciding increases in VO2 max (Levine & Gunderson, 1997). This began a storm of altitude research, even though researchers such as Faulkner et al. (1968) had been performing hypoxic exercise research since the 1960s, during which they confirmed the lower oxygen uptake by the muscle during exercise in hypoxia, leading to the physiological adaptions due to lower amounts of oxygen consumed during exercise (Faulkner et al., 1968).

Several authors have concluded that the increased production of EPO in response to a lesser amount of oxygen is a highly variable response amongst athletes in that there are some who respond greatly and can experience athletic improvements for several weeks following a training protocol, whereas some athletes do not respond because of genetic factors, and their improvements in VO2 max and performance is solely based on the adaptations from the exercise program at sea level (Płoszczyca et al., 2018). Because of this variable response of the key driving factor that stimulates erythrocyte production in the bone marrow, some researchers, including Ploszczyca and colleagues, suggest that the extra effort of traveling to altitude may be futile for some and because the adaptations of a sea level program can also increase oxygen carry capacity and improve VO2 max, maybe altitude training is not worth the athlete's and the coach's time. Is there a method that could stimulate EPO using hypoventilation and apnea, as suggested by Woorons, and incorporated into a training routine as a means to not only strengthen respiratory and abdominal strength to prevent injury and enhance longevity and cognition, but also induce hypoxic pre-conditioning (Ishida et al., 2017; Woorons et al., 2007)? Not only would this provide incredible strength to support an athlete's respiration and spinal units, but also the convenience provided with such a protocol would regain the previously lost athletic team hours traveling to either a mountain or a hypoxic chamber in the hopes of benefiting from an altitude training program. *BIIHT* is a suggested protocol that direly needs more research to investigate the possibilities (Ki et al., 2016). The intermittent exposure of hypoxia, whether during training (IHT) or during rest (IHE), is a less researched area and a much more feasible method considering it's efficiency in terms of time and cost. Therefore, IHT and IHE will be thoroughly examined in the following section, in which various modalities of varying duration, intensity, and frequency of intermittent hypoxic programs are considered.

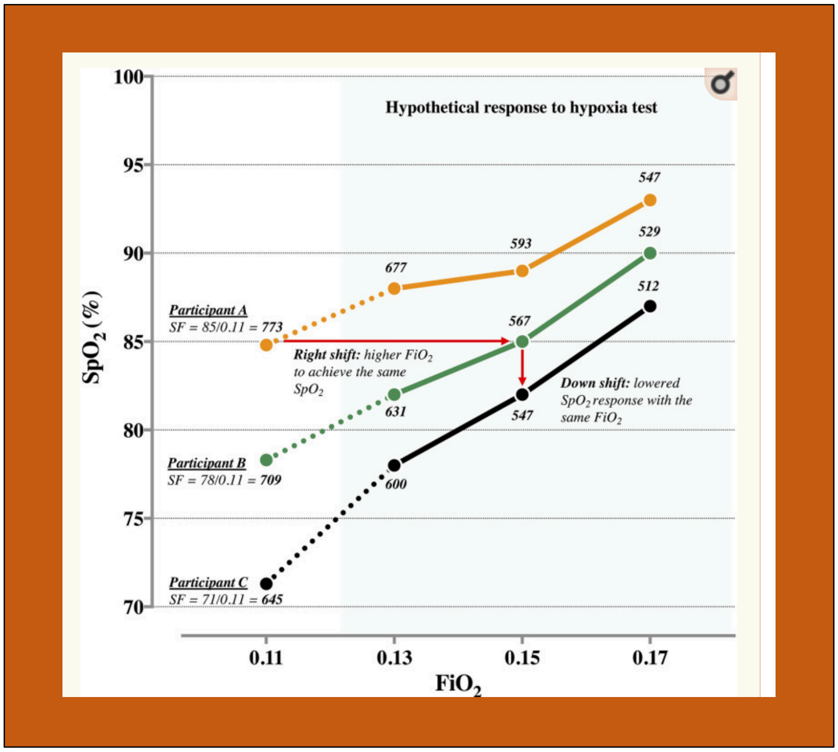
As a precursor to a discussion on the efficacy of IHE and IHT in the athletic population, an awareness of the most effective levels of altitude, with corresponding % FiO2, absent of the coinciding deleterious physiological consequences that have been documented at extreme high levels of altitude shall be discussed. Levels equal to or above 3000 meters above sea level (14.4 % FiO2) have been shown to lessen performance when training in a traditional IHT pattern of 45-90 minutes at moderate to high intensity with incidents of acute mountain sickness (AMS) exponentially increasing above 4500 meters (11.9% FiO2) (Vardy et al., 2006). At levels above 8000 meters, the negative physiological consequences increase exponentially, with a high probability of muscle and bone loss (Burtscher et al., 2018). Not only have detrimental physiological adaptations taken place in the athletes who expose themselves chronically to a severe level of altitude hypoxia, but it is also highly inconvenient to incessantly incorporate a training regimen that may include several hours of travel in order to get a training affect (Serebrovska et al., 2016).

Additionally, there is evidence that using shorter protocols using normobaric hypoxic chambers can not only increase HIF-1 to the levels necessary to increase production of EPO and erythrocyte production contributing to athletic gains, but also can result in greater hypertrophy and fat loss than corresponding control groups in hypoxia (Guardado et al., 2020; Park et al., 2016; Urdampilleta et al., 2012). Considering the efficiency of utilizing a normobaric chamber at sea level, void of the potential negative consequences of traveling to high altitude, an athlete and their coach have the option of including this in an effective training program. Furthermore, more research should be done in the area of the implementation of a breath induced hypoxic training protocol (*BIIHT*) that could be of the highest convenience if proven to provide even a fraction of the benefits of exposing oneself to altitude, whether in a normoxic chamber, on a mountain or using a mask or tent.

Using hypoxic chambers, tents, or masks have the advantage of a higher level of control in terms of time/cost efficiency and exacting the dose response relationship in a clinical setting (Torpel et al., 2019). The exact altitude above sea level can be stimulated simulated by controlling the amount of oxygen that is breathed in the air of the chamber, tent, or a mask. The FiO2, fraction of inspired oxygen, is the fraction or the percentage of oxygen that makes up the inhaled air, which is 21% FiO2 at sea level and down to 6.8% FiO2 on Mount Everest at almost 9000 meters above sea level (Richalet et al., 1992; West et al., 1983). There is a plethora of research on simulated altitude training using IHT with varying dosing at several altitude levels. The most effective altitude that has shown the least risk is 2500 meters or 15-16% FiO2 (Vardy et al., 2006). Too far above or below this number will elicit either deleterious consequences or not be enough of a training stimulus to experience an effective adaptation (Levine & Stray-Gunderson, 1997). This is another clear example of Selye's GAS model and the importance of preventing the organism from going into the exhaustion phase, which in this scenario would be represented by the athlete being exposed to altitude levels that are too extreme for too long (Selye, 1950).

The methods of hypoxic exposure at sea level have the advantage of high control in the clinical setting and ease of use, but the disadvantage is that, for the most part, this equipment is limited to a physical therapy, exercise physiology, or an academic settings (Serebrovska et al., 2016). Installation of a hypoxic chamber or tent is possible in most areas of the world, but it is not inexpensive (Wenger et al., 2015). Training masks have been proposed as another option, but has been proven to be more of a respiratory muscle strength device then and intermittent hypoxic training device due to the difficulty of respiration when wearing a mask and the unlikelihood that the SpO2 levels drop to a degree that would elicit a hypoxic training stimulus (Porcari et al., 2016) Xavier Woorons has shown in a prolific amount of studies that hypoxia can be achieved intermittently within a training session of IHT, through a method of hypoventilation, inclusive of voluntary apnea after exhalation at a low lung volume (Woorons et al., 2019). Woorons and his colleagues have observed some outstanding results in their athletic subjects inclusive of improved performance and muscle buffering capacity, both of which are highly valuable tools to the elite athlete (Woorons et al., 2008). The proposed method of *BIIHT* has the potential to elicit the adaptations that athletes experience at altitude by monitoring the athletes SpO2 levels throughout the work out, as Woorons does in his research (Woorons et al., 2007). Some researchers, such as Tetiana Serebrovska, who created the Hypoxic Training Index HTi, have performed research in the importance of monitoring an subject's SpO2 levels during the session (Serebrovskaya & Xi, 2012). The researchers reinforce that athletes should be monitored in order to prevent the blood saturation levels going too low vs not achieving a low enough SpO2 to elicit any adaptation. The authors suggest that an SpO2 of approximately 85% is aimed for in most sessions. Some researchers have been known to "SpO2 clamp" their athletes and perform a graded titrated routine that slowly acclimates an athlete to lowering SpO2 levels. Some researchers have recommended only performing using SpO2 measurements as a goal and not FiO2 based on the theory that a target SpO2 is the more important variable than FiO2 when it comes to training adaptations. See Figure 18 as a demonstration as to how three different individuals can respond to the same FiO2 levels.

Figure 18



Note: Three varying hypothetical SpO2 responses to 4 levels of FiO2, 11%, 13%, 15%, and 17%. Adapted from "The Use of the SpO2 to FiO2 Ratio to Individualize the Hypoxic Dose in Sport Science, Exercise, and Health Settings.", by Soo, J. et al. (2020). *Frontiers in physiology*, *11*, 570472. https://doi.org/10.3389/fphys.2020.570472

The missing link in a hypothetical breath induced protocol is that there would be less of an ability to personalize and titrate SpO2 levels in a training routine, but much more research needs to be done in the area of breath induced beneficial hypoxia as the convenience could possibly outweigh the ability to exact the dosing. If there is a world in which a breathing regimen can produce even a fraction of the athletic and chronic disease benefits that IHT and IHE have shown, this could foster an intermittent hypoxic training environment that is much more time and cost efficient than the current methodologies, which could contribute to not only higher levels of consistency with a program, but also opens up many more opportunities for research.

In terms of training improvements for the sub-elite or non-elite athletes, training sub-maximally, because of the shift to a glycolytic metabolism in place of the oxidative system, has the ability to garner a more intense training response than training sub-maximally at sea level without the *eustress* on the systems that “search for oxygen” such as HIF-1 and the downstream factors that are upregulated (Park et al., 2016; Płoszczyca et al., 2018). Many authors have shown an increase in glycolytic metabolism during exercise with IHT and breath holds inducing hypoxia, which can contribute to adaptations such as reduced acidosis of the blood when training to high intensity (Woorons et al., 2008). During high intensity training sessions at altitude, the live low-train high LL-TH model is an example of coaches utilizing this philosophy that an athlete must train at high intensity while at altitude or simulated hypoxia in order to achieve improvements in the anaerobic metabolism, which is highly beneficial to an athlete, who spends most of their time competing at this level (Milioni et al., 2017). Although, training at such extremes could also push the athlete into the exhaustion phase of the adaption cycle with minimal or no perceptible gains in their training based on whether they are a responder or a non-responder in terms of the EPO response (Kreher & Schwartz, 2012; Płoszczyca et al., 2018).

Therefore, based on the literature, it would seem that living high and training low would be the most effective model for stimulating a training adaptation for fine-tuned athletes. The athlete has such an elevated VO2 max and oxygen carrying capacity to begin with that it takes a big stimulus for this population to achieve a training response (Figuiera et al., 2008). It might be that for some athletes, training in hypoxia is a performance degrader due to the inability to push as hard as they would at sea level based due to changes in muscle pH and metabolites such as lactate increasing in magnitude and at a lower intensity . Most elite athletes have trained to have very high lactate thresholds to be able to perform a maximal amount of work sub-lactate threshold (Ghosh, 2004). Whereas shifting to a glycolytic metabolism during sub-maximal exercise has the advantage of fat loss, muscle gain and increased BMR for the general exerciser, the athlete has the potential of losing fitness potential because of this metabolic shift (Wehrlin & Hallén, 2006).

Based on the research that shows varying responses to the intermittent hypoxia/altitude model for the elite athlete, considering the time, expense and unknown results, until there is a genetic test that shows how an athlete's EPO in the bone marrow is going to respond to a hypoxic treatment, the elite athlete and their coach might consider alternative, more efficient training methods. Xavier Woorons has shown in several studies an improvement in sprint time, swim time, and cycle time, in addition to increases in lactate, quicker drops in pH, and adequate drops of SpO2 levels to achieve intermittent hypoxia with the hypoventilation method (Woorons et al., 2008; Woorons et al., 2007; Woorons et al., Woorons et al., 2020). In one of the studies, the authors state that while these athletes did see improvements in their performance, much more research needs to be done in this area, and the level of discomfort that an athlete must endure when holding their breath while performing high intensity exercise is most likely something only a small percentage of the population, indicative of the determination of a high caliber athlete, would be willing to endure (Woorons et al., 2007).

Inspired by Woorons, more research should be performed in the area of slow breathing, forced exhalations and voluntary apnea protocols to benefit the mind and body of the athlete or the general population exerciser. There may be benefit to athletes performing breath training induced intermittent hypoxia (*BIIHT*) in order to achieve the low doses of SpO2 within the workout that mimic 30-90 seconds of acute intermittent hypoxia as is demonstrated in the spinal cord injury motor plasticity studies of Trumbower, Mitchell, and Naverrete-Opazo, but there is a paucity of breath induced hypoxic research. This leaves the door open for the possibility of future research that could lay the groundwork for achieving athletic results without having to climb a mountain or travel to a hypoxic chamber.

5.2 The Sub-Elite & General Exerciser

Sub-elite and non-elite, general population exercisers, whom encompass a much larger percentage of the world-wide population, do not have the finely tuned machines that elite athletes do and therefore respond much more easily and quickly to training in hypoxia (Hughes et al., 2017). Because the general population has a lower VO2 max, lower hematocrit, lower hemoglobin and coinciding lower oxygen carrying capacity, they are able to have a more powerful training stimulus (Mairbäurl, 2013). The general population, who may not have the high functional capacity that an athlete has, may not be able to train in the "high intensity" energy system that allows them to see maximum adaptations from exercise (Foster et al., 2015). It is for this population that training in hypoxia has the ability to make drastic improvements in VO2 max, red blood cell capacity, and increased oxygen uptake capacity as the hypoxia shifts the sub-maximal exerciser from working the oxidative system to the glycolytic system during a less intense exercise session (Murray, 2009). Even though the body is working at a low intensity, the body is perceiving a more intense effort and therefore, causes enough of a *eustress* to cause a positive adaptation from the more intense stimulus requiring the organism to be able to better handle the stressor (less oxygen) during the subsequent exposure (Selye, 1950).

Increases in motor-unit recruitment, fast twitch muscle fiber use, and increases in post-exercise lipolysis, due to the increased amount of catecholamines during a sub-maximal workout, give the general population exerciser the ability to experience positive feedback in terms of strength, oxygen uptake and body composition, based on their sub-maximal approach to daily exercise (Urdampiletta et al., 2012). The irony of these statements is that it is the elite athletic population, who has the time and expense to devote their lives to an intermittent hypoxic training regimen, as it is their full time job to optimize their minds and bodies to prepare for competition. The majority of the people on the globe who consider themselves general population exercisers do not have the extra time or the money to devote to a methodology that might help to optimize their results when they are barely squeezing a jog and a minimum effective dose weight training program. Considering that more than half the globe is diagnosed with two or more chronic diseases, and adding hypoxic training into one's training program has the potential to produce a more efficacious workout in terms of motor skill learning, fat loss and chronic disease reduction while working at a sub-maximal, injury preventative level, there is need to further explore the creation of a more convenient and cost effective method of enabling general exercisers to participate in a form of hypoxic training (Hajat & Stein, 2018). IHT has also has shown to have the ability to increase the amount of muscle, inclusive of fast twitch muscle fiber, which is the key muscle type that begins to atrophy and contributes to sarcopenia as we age (Guardado et al., 2020). Jung et al. (2021) present a convincing case for the use of resistance training in hypoxia as a method to battle the epidemic of sarcopenia in aging. The authors argue that older individuals are not able to achieve the 70-80% of one repetition maximum that is recommended by national strength organizations in order to achieve increases in muscle mass, bone density and strength (Jessee et al., 2018). Therefore, the use of sub-maximal training (at levels of 40-50% repetition max) in a hypoxic environment is feasible for an elderly exerciser.

Again, the barrier to implementation of hypoxia is convenience. Especially for the individual who is working a full time job, the extra travel time and expense that it takes to implement a routine such as this is highly unlikely. The elite athletic hypoxia training paradox is an interesting one that needs to be further explored. If a specific breath training routine had the ability to achieve short doses of hypoxia with increased motor unit recruitment, type II muscle fiber recruitment, and metabolic stress to the muscle, would the globe see less sarcopenia, one of the leading precursors of not only body composition changes with the associated exponential muscle loss with age, but also lower rates of osteoporosis and cognitive decline through the maintenance of muscle mass (Jung et al., 2021; Tolea & Galvin, 2015)?

In a study examining the effects of IHT on muscle hypertrophy, the authors observed a muscles mass increase that was 5.5x greater than that in normoxia and a fat loss that was 6.5x greater than in normoxia (Guardado et al., 2020). This experiment was performed in an untrained population, which would explain their substantial improvements, but the improvements in the normoxia group were not nearly as substantial. The training regimens, even though classified as hypoxic, were of continuous exposure for the entirety of the weight training program 3x/week. Therefore, these longer durations of 45-60 minute at 13% FiO_2 would not be able be achieved with short 30-90 second dips in SpO_2 as is recommended with a breath induced training protocol, but some authors have used shorter, more intense protocols to elicit positive change in the IHT protocols. For example, Susta et al. (2017) showed an improvement in the sympathovagal tone and improved exercise performance of a group of athletes with overtraining syndrome, exposing them to 10% FiO2 for shorter protocols. Furthermore, a group of elderly individuals with stable angina was exposed to 12% FiO2 for 5 minute protocols, which resulted in improved exercise tolerance and lipid metabolism (Korkushko et al., 2010). That being said, there are just a handful of studies at shorter doses of hypoxic training protocols in terms of creating the metabolic stress necessary for the muscle to warrant adaptation. Kon et al. (2014), using moderate amounts of intensity averaging at 65% of one rep max, showed increases in human growth hormone, GH, and testosterone, after the hypoxic training protocol. Current day exercise science research suggests high intensity strength training protocols such as 80-90% of one rep max to elicit anabolic hormonal surges of testosterone, and HGH (Mangine et al., 2015). Because the elderly and the lesser trained general population does not have the strength to prevent injury at this magnitude of intensity, the evidence points to the fact that intermittent hypoxic training is a training regimen, in which the general population exerciser and untrained individual could have an advantage.

Athletes need to train sport and skill specific in order to train their physiology to be more adept at that skill (Reilly et al., 2009). An athlete needs to train with high intensity in order to perform at high intensity and the same is true for endurance training (Häkkinen et al., 1989). If hypoxic exposure limits the intensity that the athlete can train at, long-term exposure could be detrimental to the specificity needs of the athlete. The individual who does not need to or is not physically able to train at high intensity, has the ability to train at a low or moderate intensity and achieve some of the benefits with the hypoxia induced metabolic stress and anabolic hormones that an athlete can experience (Jung et al., 2021). The range of FiO2 in the IHT sessions ranges between 12-16%, and the duration is generally 20-60 minutes, 3x per week (Park et al., 2018; Viscor et al., 2018). Shorter protocols, as mentioned above, have not been as intensely studied. If shorter hypoxic exposures, induced by a combination of forceful exhalations, slow exhalations, and voluntary apneas intermittently throughout the workout could produce just a fragment of what has been shown in the longer exposures of IHT research, this opens up the world of higher rates of strength and endurance from exercise programs with the ensuing consistency of a program. Much more research is needed in this area to disentangle the appropriate dosing for maximum benefit from hypoxic sub-maximal exercise. The global sarcopenia epidemic, leading to the precursors of accelerated morbidity of cognitive decline, bone loss and fat gain, impose a dire need on creating structured intermittent hypoxic protocols that are more accessible, while maintaining efficacy (Tolea & Galvin, 2015).

5.3 Motor Learning

In terms of motor plasticity and potential motor learning enhancements for athletes and general population exercisers, Dale et al. (2014) reinforce that not only does motor plasticity occur in the respiratory muscles in which HIF-1 increases in order to encode the growth trophic factors that increase ventilation in order to maintain homeostatic oxygen levels, but this also occurs in non-respiratory motor neurons, which can aid in improving motor control in other areas of the body that may have been affected by stroke or spinal cord injury. More research is needed in the area of non-respiratory motor improvement as this is an area that could benefit athletes and general exercisers looking to refine their skill with improved motor learning connections. If BDNF is upregulated in response to low oxygen and increases the activity of the motor neurons that improve not only respiratory, but also non-respiratory muscle connections in those with SCI, would athletes be able to improve their form in a squat or have better core control in all movements with this injury preventative and sports enhancing modality? These questions are worthy of disentangling as they could have profound implications for both the diseased and the healthy population.

Trumbower et al. (2012) found that ankle plantarflexion increased in strength after the SCI patients were exposed to intermittent hypoxia. Another SCI study found that walking speed and endurance improved after training gait in an intermittent hypoxic cycling program of 9% FiO2 alternating with normoxia (Hayes et al., 2014). Navarrete-Opazo et al. (2017) also found with a 9% acute hypoxic cycling protocol that the subjects with SCI were able to improve the mechanics of walking. The importance of this research in the area of SCI, in which motor function is highly limited, is of vital importance, as for some, this is the only protocol that is giving them a “window of opportunity” to effectively move parts of their body that have been otherwise limited from the spine injury that controls their movements. After prioritizing the SCI population in this area of research, an area that could be an envisage of opportunity for research and professional athletics is the potential for intermittent hypoxia positively enhance motor function both in the professional athlete and the general population exerciser. Not only could this enhance performance, but also reduce the risk of injury from poor biomechanics in movement (Hewitt & Bates, 2017). Can motor skills be improved with intermittent hypoxic protocols in the athletic and general population simply seeking better movement quality and skill retention? Woorons and his colleagues have made it very clear that athletic improvements are possible with hypoxic exposure from breath holds, but this is due to the metabolic changes that happen in hypoxia in terms of lactate and muscle buffering in an anaerobic state (Woorons et al., 2020). Can athletes benefit from an increased amount of serotonin and BDNF from hypoxic exposure that would then potentiate connections between spine and brain leading to more efficient learning of movement and long term retention of skill? If an slow exhalation, forced exhalation and voluntary apnea pattern could contribute to spikes in BDNF and serotonin in order to enhance motor functioning during and after a training session, that would open up a world of potential for both the elite and non-elite athlete alike.

5.4 Using Breath to Enhance Athletic Potential

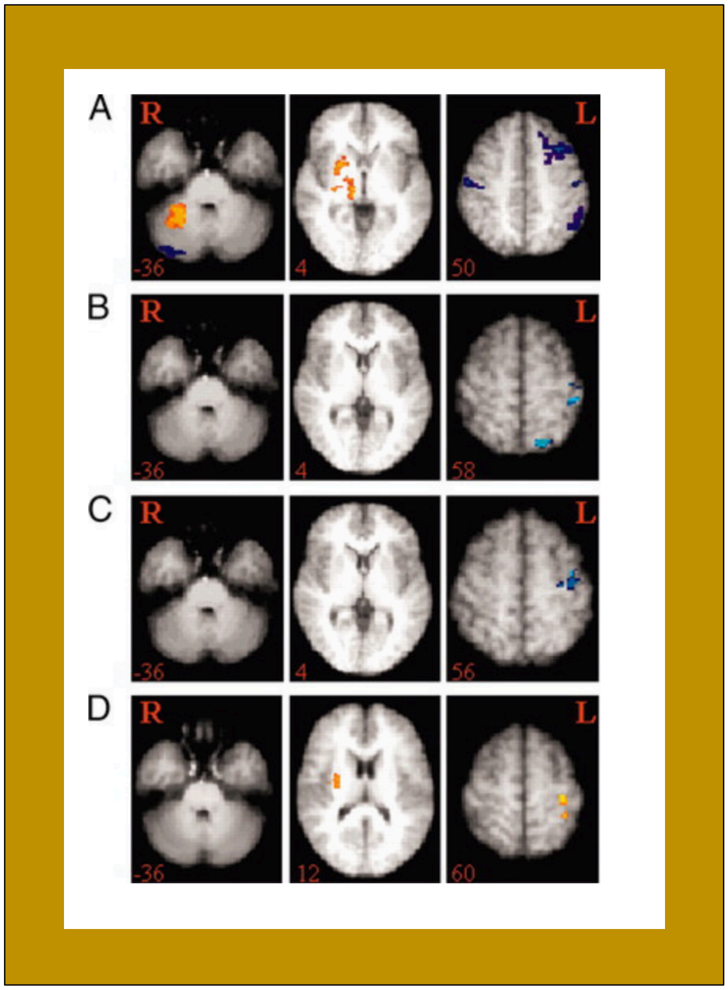
Not only does HIF-1 upregulate factors such as EPO and VEGF, which have been shown to greatly improve motor function via increased blood cells and angiogenesis, but the chemoreceptors, triggered from rising CO2 levels in the blood as oxygen levels go down, trigger serotonin release which upregulates BDNF, another growth factor contributing to improved brain and somatic function (Dale et al., 2014; Naverrete-Opazo & Mitchell, 2014). Even though these growth factors stem from different sources, they both trigger a cascade of motor benefits stemming from the lower oxygen levels that the body is exposed to (Tehran et al., 2014). An interesting aside concerning chemoreceptors is these receptors are stimulated by rising CO2 levels, which are inversely proportional to oxygen levels in the blood (Benner et al., 2020). Hypoventilation, or breathing with slow breaths inclusive of breath holds, induces hypercapnia, which is the raised levels of CO2 in the blood (West, 2011). Could it be that chemoreceptors are triggered to a high enough level during the hypercapnic event of hypoventilation that serotonin is released and BDNF is upregulated? This would be implicit of improvements in motor learning during and post-training session due to this growth factor being upregulated simply by manipulation of the breath. This is a bright area worth of more research.

Hypothetically speaking, if the breath training protocol of *BIIHT* were used to implement an IHT regiment, there are a plethora of advantages for both the athlete and the non-athlete alike implementing breath training within their workout. IHT aside, incorporation of voluntary breath control intra-workout has the benefits of reducing anxiety and therefore improving accuracy via upregulation of the parasympathetic nervous system, increased recruitment of the core abdominal muscles with subsequent reduction of risk of injury, increased HRV scores with increased injury-preventative recovery rates and increased motor skill learning retention contributing to athletic competitive success and lower injury rates with higher quality motor skills of functional movements in the general population (Czuba et al., 2019; Larson et al., 2020; Russo et al., 2017). An increased HRV means higher parasympathetic nervous system activity and lower sympathetic nervous system activity for increased blood flow and vasodilation within the muscle as the parasympathetic nervous system dilates the blood vessels and increase blood flow (Sheng & Zhu, 2018). Slow breathing, therefore, has the ability to improve the strength, mobility and endurance of a muscle via increased perfusion, or blood flow, within the muscle with a higher HRV score that represents a parasympathetically dominant tone (Carravieri et al., 2016). Hypertensive research using intermittent hypoxia protocols have shown increased sympathetic nerve activity in the musculoskeletal system, which vasoconstricts the muscles, limiting blood flow (Esler, 2000). Blood flow to the muscle is called muscle perfusion , and the higher the muscle perfusion during and after exercise, the healthier the muscle in terms of mobility, strength and power (Delp & Laughlin, 1998). An improved HRV will not only improve the relationship between the two halves of the autonomic nervous system (ANS), but will also improve muscle health because of the improved regulation of vasoconstriction and vasodilation that the ANS controls (Tyagi & Cohen, 2016). If a breathing protocol could lead to improvements in not only the health of the muscle, but also induce the other known benefits of intermittent hypoxia, the world of HRV and hypoxic training would be much more accessible to all individuals.

The research supporting the use of exercising with voluntary breath control is plentiful and lays a solid groundwork for more research to show that an additional element of the importance of prioritizing HRV and potentially intermittent hypoxia into a training protocol. For example, the internal obliques, external obliques and transversus abdominis have been shown to greatly increase in recruitment when performing a forceful exhalation in conjunction with traditional core exercises such as plank and curl up (Boyle et al., 2010; Ishida et al., 2017; Oh et al., 2020). Increasing the recruitment of the obliques and the transversus abdominis, which acts as a corset for the spine with a "belt-like" circumference of tension connecting into the lumbar thoracolumbar fascia, has been shown conclusively to reduce the risk of low back injury, which can be devastating in its recovery rate and pain scale for the athlete (da C Menezes Costa et al., 2012). If indeed an intermittent hypoxic training element can be added to a training regimen, the potential spike in BDNF in the non-respiratory muscles can elicit increased motor neuron activity to improve the form and function of the exerciser. Satriotomo et al (2014) demonstrated the potential for non-respiratory muscles to increase in activity due to the downstream effects of HIF-1, inclusive of an increase in ERK and AkT activity, contributing to an increase in motor neuron activity with subsequent improvements in strength through the increase in somatic motor neuron activity (Satriotomo et al., 2012). The aforementioned results have not been published, and this is a perfect example of the dire need for a stronger focus in this area in order to dig deeper into the area of intermittent hypoxia research in the area of motor control.

If slow breathing were utilized in a *BIIHT* protocol to induce IH and core function, an increase in motor learning is a strong possibility as the cross-talk between the cerebellum, basal ganglia, primary motor cortex, posterior parietal cortex and dorsolateral prefrontal cortex when both voluntary controlling the breathing and motor learning of new skills has a high correlation (Yadav & Mutha, 2016). The activity in these areas that promote strong motor learning also are strengthened and increase in activity when slowing the breath down (Floyer-lea & Matthews, 2005). Therefore, if studies on intermittent hypoxia that show an improvement in motor learning were combined with the research protocols that show an improvement in motor learning with slow breathing, could there be compounded, exponential improvements in motor learning for both those with chronic disease or injury of the spinal cord and healthy exercisers alike (Tan et al., 2021)? The combination of voluntary breathing during exercise with a combination of IH, whether induced by breath, altitude, or hypoxic chamber, is an under-researched area that must be explored more deeply in order to enable those with exercise prescription authority the ability to more effectively guide their clients, patient and athletes with appropriate protocols with enhanced motor learning.

Figure 19



Note: Increased motor learning while integrating voluntarily slowed breathing during exercise through activation of the cerebellum, basal ganglia, primary motor cortex, posterior parietal cortex and dorsolateral prefrontal cortex. Adapted from "Distinguishable brain activation networks for short- and long-term motor skill learning.", by Floyer-Lea, A., & Matthews, P. M. (2005). *Journal of neurophysiology*, *94*(1), 512–518. https://doi.org/10.1152/jn.00717.2004

5.5 Contraindications

Altitude Mountain Sickness, AMS, is the development of symptoms such as headache, nausea and dizziness due to exposure to altitude (Parati et al., 2018). Experts recommend to pre-acclimatize in order to condition oneself to high altitudes or the corresponding simulated altitude in a chamber, tent, or hypoxicator (2500-3500 meters, 15-14% FiO2) by using a lower, intermediate exposure (300-2500 meters, 20.1-15% FiO2) for a period of time in order to prevent the onset of AMS (Burtscher et al., 2018; Lopata & Serebrovskaya, 2012). For very high altitudes of above 3000 meters and 14% FiO2, a recommended strategy of 1-4 hours per day for approximately 1 month time of simulated altitudes of 4000 meters (13% FiO2) is suggested to reduce the onset of symptoms, but because this paper is focusing on protocols of 2500 meters (15% FiO2) and less for the purposes of athletic improvement, chronic disease prevention and therapy, and anti-aging, these extremes are not necessary for optimization (Burtscher et al., 2008).

The majority of the literature reinforces that most individuals who experience AMS are at altitudes above 2500 meters (15% FiO2) (Meier et al., 2017). Therefore, the likelihood of developing AMS if using protocols below 2500 meters is statistically low if not non-existent (Vardy et al., 2006). If using protocols above 2500 meters, an acclimatization of no more than 300 meters (1% FiO2) per day of ascent is highly recommended in order to reduce the likelihood of AMS symptoms (Verges et al., 2015). Additionally, exposure to normobaric hypoxia in a hypoxic chamber, coinciding with normal air pressures, vs hypobaric hypoxia, coinciding with low air pressures as experienced when climbing a mountain, has been shown to greatly decrease the likelihood of experiencing AMS as many researchers have correlated the changes in pressure to being a stronger correlating factor with AMS than the changes in oxygen saturation of the blood (Roach et al., 1996). Therefore, one may consider training in a normobaric hypoxic chamber in contrast to climbing a mountain in order to prevent the uncomfortable symptoms of the low pressures of altitude (Ptak et al., 2103). The plethora of research that has shown positive adaptations in the areas of athletic enhancement, obesity, and chronic disease when exposed to normobaric hypoxia, prove that hypobaric hypoxia is not deemed necessary to achieve positive outcomes (Serebrovska et al., 2016). Because of the additional convenience that exposing oneself to normobaric vs. hypobaric hypoxia affords is notable and allows for greater consistency in a long-term training regiment.

Because it is the individual response to the environment, which is the shift in SaO2 levels, not the level of oxygen in the air or the amount of pressure, that has been proven to be the most important factor in the positive outcomes of the dose-response relationship, it is recommended that these levels are monitored, especially in a pre-conditioning period, in order to titrate an appropriate environmental dose to support the individual maintaining an SpO2 of approximately 85% during training sessions (Basnyat, 2018; Lopata & Serebrovskaya, 2012). Too far below this could cause uncomfortable consequences, while too far above this could minimize any additional training effect outside of the positive adaptions from the exercise training program (Soo et al., 2020). The Hypoxic Training Index takes into account the FiO2 and SpO2 in an equation that gives the coach, researcher, and trainee feedback as to the individualized response to the training protocol (Serebrovskaya & Xi, 2012). Additionally, SpO2 clamps have been suggested as a means of monitoring and personalizing hypoxic training session (Soo et al., 2020). That being said, most research has been comfortably set at between 12-15% FiO2, much of which has not recorded SpO2 levels, and a multitude of positive adaptions have been observed in the areas of athletic performance, obesity, hypertension, type 2 diabetes, metabolic syndrome, cognitive enhancement, osteoporosis, cardiovascular disease and central nervous system disorder with little to no risk (Mateika et al., 2014).

Even though improvements have been witnessed in all of these areas with a moderate dose of 15% FiO2 and 2500 meters in normobaric chambers, it is advised that a prospective intermittent hypoxic trainee consults with their doctor if they have a history of heart disease, hypertension, stroke, or lung disease (Parati et al., 2018). Furthermore, pregnant women and those with sickle cell disease are contraindicated for this type of training (Khodaee et al., 2016). In terms of the possibility of using a *BIIHT* protocol to induce intermittent hypoxia, there are contraindications in this area as well. Anyone with a history of heart disease, lung disease, hypertension, detached retina or pneumothorax should consult with their doctor before performing these breathing exercises due to the effect that any breathing exercise, including various forms of pranayama, can have on the central nervous system and cardiovascular system (Nivethetha et al., 2016). For the majority of the population, the benefits drastically out weigh the risks and with a moderate dose of altitude of less than or equal to 2500 meters above sea level (15% FiO2) there is little to no risk of AMS or other deleterious consequences unless a predisposing health condition limits positive adaptations (Vardy et al., 2006).

It has been suggested that those with a resting SpO2 of less than 95% are more likely to have AMS and other deleterious consequences from this style of training and therefore, should consult with their doctor if beginning an IHT, IHE, or breathing training protocol (Parati et al., 2018). Moderate protocols of intermittent hypoxia have been touted as a low-risk therapeutic tool for the use of those who fall into the categories of both healthy and those with comorbidities, as it is the intermittent hypoxia protocols that have helped many with disease reduction (Dale et al., 2014). That being said, many of the same diseases that IHT and IHE have been shown to benefit, also are said to be contraindications (Mateika et al., 2014).

Therefore, if considering any of the aforementioned protocols, advice from a doctor is recommended prior to embarkation. Additionally, minimum effective dose is highly recommended in order to maximize the dose-response relationship without pushing into the exhaustion phase of these protocols. Because research has shown that both athletes and those with chronic disease continue to observe positive adaptations for many weeks following a protocol of 4-8 weeks, periodizing the application of intermittent hypoxia, in a similar fashion to the way that a standard periodized exercise program would be delivered in terms of frequency, duration and dose, is recommended (Lorenz & Morrison, 2015; Manukhina et al., 2016). For example, applying a moderate dose of 15% FiO2 (2500 meters) for a one month period, followed by one month of lower levels or sea level training, over the course of the yearly macrocycle could be an effective strategy that allows for recovery intermittently, while also maintaining conditioning (Serebrovskaya et al., 2016). For example, if one were to use a standard pre-acclimatization strategy of increasing no more than 300 meters, 1% FiO2 of elevation each day, to gradually elevate to a point of 2100-2500 meters over a slow acclimatization period of one month, this could serve as not only an initial pre-conditioning period to prepare the individual for more intense training protocols over the following month, but also could serve as the reset/recovery period after a 4-8 week period of training at higher altitude/lower FiO2 levels. Following a training protocol such as this over the course of the year could support maximizing positive adaptions and reduce the risks of maladaptations (Naverrete-Opazo & Mitchell, 2014).

In terms of specific duration, frequency, and intensity, there is a wide range of suggested doses within the area classified as a moderate, adaptive (beneficial) dose vs. a chronic, severe (maladaptive) dose (Verges et al., 2015). A range of between 9-16% FiO2, 3-15 cycles, and durations of 15 seconds – several hours have shown to mostly produce beneficial results (Navarrete-Opazo & Mitchell, 2014). Detrimental doses, such as those seen in sleep apnea and extreme, altitudes of greater than 6000 meters above sea level, which represent FiO2 set at approximately 5% with cycles being greater than 50 cycles per day, are not recommended for beneficial adaptations as these severe cycles push the organism into the exhaustion phase with maladaptations such as increased free radical production and inflammation (Lavie, 2003; Lavie, 2015; Navarrete-Opazo & Mitchell, 2014; Serebrovska et al., 2016 ; Verges et al., 2015).

In terms of integrating a breathing protocol such as *BIIHT* during the hypoxic training protocols, it has been shown that not only are adaptions enhanced such as HIF-1 levels and improved HRV intra and post-training session, but also the respiration strength that coincides and acts to support anti-aging, is significant and is recommended for implementation (Zaccaro et al., 2018). If indeed more research is performed in the area of breath induced intermittent hypoxia protocols, an at home version of simulating various altitudes by performing various frequencies, durations and intensities of the breathing routine could be an effective strategy for implementing an at home periodized routine over the course of the year. Challenging the strength of the respiratory muscles and the metabolic, bioenergetic, and cardiovasular/nervous system markers that coincide with performing forceful exhalations, slow breathing and breath holds need to be further evaluated so that more specific recommendations can be made for a convenient at home breath induced intermittent hypoxic training protocol that would allow for not only positive adaptations, but also the necessary recovery that would be prescribed in a traditional, effective sports periodization program (Lorenz & Morrison, 2015; Verges et al., 2015). More research is certainly needed on the dosing and application of a breath induced intermittent hypoxic training protocol, but a future inclusive of more research in the area of intermittent hypoxic training and periodizing a breathing program for the purposes of increased vitality and anti-aging is a bright one!

CHAPTER 6

IH DOSING IN THE LITERATURE

6.1 IHT & IHE Dosing Chart, A Literature Perspective

With a wide range of dosing of successful IHE and IHT protocols, it is clear that more research is needed on the most successful protocol in each of the areas of athleticism, chronic disease and spinal injury. That being said, there is a certain window that is considered beneficial of less than 15 hypoxic cycles per day and between 9-16% FiO2 (Navarrete-Opazo & Mitchell, 2014). Most OSA sufferers experience upwards of 1,000 hypoxic cycles, which is highly damaging to inflammatory markers and contribute to high blood pressure and other chronic diseases (Sforza et al., 2016). Inhaling below 8% FiO2, which correlates with extreme high altitude heights of higher than Mount Everest, have been shown to be detrimental to one's health, including bone and muscle loss (Murray, 2009). Hans Selye would agree that a moderate intensity of 9-16% with a moderate frequency and duration of 3-15 cycles would allow for a positive adaptation to take place without pushing the organism into a distressed stress that is not conducive to recovery and hence adaption.

Table 3

Study	Frequency and Duration	Intensity	Results and Method (IHE vs IHT)
LUNG			
Cai et al., 2021	6-10 x 3-5 minute cycles; 3-5 times/week; 8 weeks	16% FiO2; 2200 meters	This is a proposed protocol by the authors for Covid-19 based on the current research on the pandemic and intermittent hypoxic treatment strategies, IHE and IHT
Haider et al., 2009	3-5 x 3-5 minutes cycles; 5 times/week; 3 weeks	12-15% FiO2; 4550-2450 meter	Balanced autonomic dysfunction in COPD patients, IHE
Rosova & Mankovska, 2012	5 x 15 minutes; 7 days/week; 4 days	12% FiO2; 4550 meters	Normalized lung ultra-structure of heart, improved blood-air lung barrier, and promote beneficial mitosis in lung and heart tissue of Wistar rats, IHE
Vogtel and Michels, 2010	15 sessions in 4 weeks	12-15% FiO2; 4550-2450 meters	A group of COPD patients improved FEV, FVC and carbon monoxide diffusing capacity, IHE

Segovia-Juarez et al., 2020	Living high at altitude	13% FiO2; 3500 meters Peru	Significantly low percentage of cases and increased recovery times in the individuals who live at altitude based on lower number of ACE2 receptors in lungs
Aboubakr et al., 2001	10 x 3 minute hypoxia; 2 nights once before and once after CPAP treatment	8% FiO2; 7700 meters	Long-term ventilatory facilitation in OSA patients; IHE
Rowley et al., 2007	10x 3 minute hypoxia; 1 night	8% FiO2; 7700 meters	Reduced upper airway closure in OSA patients, IHE
Serebrovskaya et al., 1999	3 x 7 minute cycles; 15 days	11% FiO2; 5100 meters	Increased alveolar ventilation and lung ventilation in healthy subjects and increased hypoxic ventilatory threshold in hyperpnea subjects
Berezovsky et al., 2015	3 x 15 minutes; 7 days/week; 2 weeks	12% FiO2; 4550 meters	Alleviated bronchospasm, IHE

Burtscher et al., 2009	3-5 x 3-5 minutes cycles; 5 times/week; 3 weeks	12-15% FiO2; 4550-2450 meter	Improved exercise tolerance in patients with COPD, IHT
CARDIOVASCULAR DISEASE			
Burtscher et al., 2004	3-5 x 3-5 minute cycles/day; 15 days	10-14% FiO2; 6000-3250 meters	Middle-aged men with myocardial infarction increased hematocrit, oxygen carrying consumption, lowered resting heart-rate, and rate of perceived exertion during exercise, IHT
Korkushko et al., 2010	4x5 minute cycle; how long?	12-14% FiO2; 4550 – 3250 meters	Elderly patients with angina reduced symptoms, improved lipid metabolism, and increased exercise tolerance, IHT
Aguilar et al., 2018	4x1 cycle, 4 days	11.7% FiO2; 4450 meters	Improved the anti-oxidant defenses in the endothelial cardiovascular dysfunction of rats
Zhang et al., 2014	5 x 4 minute cycles; 14 days	10% FiO2; 6000 meters	Enhanced arterial O2 delivery and improved HRV after exposure; IHE

Shatilo et al., 2008	4 x 5 minute cycles; 5 cycles per day; 4 weeks	12-14% FiO2; 4550 – 3250 meters	Reduction in angina symptoms, improved lipid metabolism, inrease exercise tolerance in angina patients, IHT
HYPERTENSION			
Mukharliamov et al., 2006	10 x 5 minute cycles; 10 days	10-14% FiO2; 6000-3250 meters	Improved efficacy of blood pressure medication and reductions in systolic and diastolic blood pressure, IHT
Lyamina et al., 2011	4-10 x 3 minute cycles	10% FiO2; 6000 meters	Increased production and synthesis of endogenous NO, improving hypertension, IHE
Muangritdech et al., 2020	8 x 3 minute cycles; 3 times per week; 6 weeks	14% FiO2; 3250 meters	Both IHE and IHT groups lowered blood pressure and raised HIF-1 and NO levels. IHT was more effective, IHE & IHT
Aleshin et al., 1993	30 minutes per day; 5 days per week; 3 weeks	13.5% FiO2; 3500 meters	Blood pressure lowering in patients
COGNITIVE			

Critchley et al., 2015	1x4 hours/day; 4 weeks	13% FiO2; 3250 meters	Increased activity in several areas of the brain related to cognition, IHT
Schega et al., 2013	4 x 10 minutes cycles/day; 3 days/week; 6 weeks	FiO2 adjusted to individual's SpO2 response (90-80% over 6 weeks)	Improved cognition in group of elderly persons. IHT
Schega et al., 2016	1 x 90 minutes IH exposure; 3 times per week; 4 weeks	FiO2 adjusted to the SpO2 between 90 and 85% and from the second to the fourth week to 80%	Increased cognition (Stroop Test), physical performance and hematological parameters
SPINAL CORD INJURY			

Trumbower et al., 2012	15 x 60-90 seconds, single session	9% FiO2; 6800 meters	Increased strength of ankle plantar flexion implying improved somatic motor output in SCI patient, IHE
Hayes et al., 2014	15 x 90 seconds; 5 days	9% FiO2; 6800 meters	SCI patients improved their walking speed and distance, IHT
Tester et al., 2014	10 x 2 minute cycles; 10 days	8% FiO2; 7600 meters	Increased ventilatory long-term facilitation in SCI patients, IHE
BONE			
Oishi et al., 2016	7-8 x 20/hour; 7 days/week; 3 weeks	4% FiO2; 11,500 meters	Microarchitecture and mineral density of rats improved alongside significant increases in VEGF, HIF-1A, ALP, IHE
Bin-Jaliah et al., 2010	10 x 6 minutes; 1 session	10% FiO2; 6000 meters	Increases in red blood cells and EPO to heart, which increase oxygen transport capacity, IHT
Huang et al., 2011	1x5 hours/day; 5 days/week; 5 weeks	11.75% FiO2; 4500 meters	Increased BMD (bone mineral density) in rats, IHE

Arnet et al., 2003	1x4 hours/day; 7 days/week; 2 weeks	12.7%-14.4% FiO2; 3000-4000 meters	Increased BMD and BMC (bone mineral content) in rats, IHE
Hung et al., 2012	24 hours/day; 21 days	14.4% FiO2; 4000 meters	BMC decreased after bed rest (IHE) and increased BMC after walking protocols (IHT)
Swanson et al., 2015	1x1 hour/day; 2 days/week; 7 weeks	15% FiO2; 2450 meters	No changes in BMD, IHT
Ramos et al., 2015	24 hours/day; 24 weeks	15.3% FiO2; 2500 meters	Decreased BMD in the hikers, IHT
Sforza et al., 2013	8 hours/night	5-8 % FiO2; 8000 meters	Increased BMD in OSA patients, IHE
Zhang et al., 2020	1 x 6 hours; 7 days/week; 8 weeks	10 – 11% FiO2; 6000-5100 meters	Improved fracture healing time including BMD, bone stiffness, expression of bone healing markers such as RUNX2, osterix, and type 1 collagen were evidenced. Significant increase in HIF-1 and the downstream VEGF.

OBESITY			
Kong et al., 2014	1 x 2 hour sessions/day; 3 times/week; 4 weeks	14.5-16.4% FiO2; 3000-2000 meters	IHT causes more weight loss in obese young adults than normoxia, IHT
Netzer et al., 2008	1x90 minutes/day; 3 times/week; 8 weeks	15% FiO2; 2450 meters	More fat loss in obese population than the control group, IHT
Workman & Basset et al., 2012	1 x 3 hour session; single day	Target SpO2 of 80%	Increased resting energy expenditure and lipid utilization, IHE
ANXIETY DEPRESSION			
Kushwah et al., 2016	1 x 4 hours/day; 2 weeks	11.2% FiO2; 5000 meters	Reduced depression and increased BDNF in rat hippocampus, IHE
Zhu et al., 2010	1 x 4 hours per day; 14 days	11 % FiO2; 5000 meters	Reduced depression and increased neurogenesis in rat hippocampus, IHE

Ding et al., 2019	1 x 4 hours per day; 14 days	11% FiO2; 5000 meters	Increased VEGF, BDNF and HIF-1 for relief of PTSD in mice, IHE
METABOLIC			
Serebrovska et al., 2016	1x3 hours/day; 7 days/week; 22 days	460 mmHg hypobaric chamber	Reduced blood sugar by 21.3%, IHE
Serebrovska et al., 2019	4 x 20 minute cycles; 9 sessions	12% FiO2; 4550 meters	No detrimental effect on the SpO2 of those with diabetes; regulation of blood insulin levels
Tian et al., 2016	1 x 6 hours/day; 3 weeks	11.1% FiO2; 5050 meters	Increased anti-oxidant pathways and HIF-1a upregulation, which protected the kidneys in diabetic rats
Wiesner et al., 2010	1x60 minutes/day; 3 times/week; 4 weeks	15% FiO2; 2450 meters	Improved VO2 max, time to exhaustion, and body composition, IHT
Mackenzie et al., 2012	1x60 minute single session	15% FiO2; 2450 meters	Type 2 diabetics who participate in 60 minutes of continuous exercise at 90% lactate threshold lowered short-term and

			long-term blood glucose and insulin sensitivity, IHT
ATHLETE			
Torpel et al., 2020	8 strength exercises; 4 times per week; 5 weeks	13.5% FiO2; 3500 meters	Increases in red blood cells with increases in EPO both centrally and peripherally, IHT
Guardado et al., 2020	1x1 hour session; 3 times per week; 7 weeks	13% FiO2; 3250 meters	Greater increase in muscle mass and loss in fat mass over control group, IHT
Czuba et al., 2018	1 x 90 minute session; 3 time/week; 4 weeks	16.3% FiO2; 2000 meters	Increased VO2 max and aerobic capacity, IHT

Note: Dosing of IHT, IHE, and OSA and the

POSITIVE ADAPTATIONS VS NEGATIVE MALADAPTATIONS

CHAPTER 7

COGNITION

7.1 Intermittent Hypoxia, Dementia, & Alzheimer's Disease

Almost 50 million people worldwide are currently diagnosed with dementia, and those numbers are predicted to rise at an alarming rate to close to 150 million by the year 2050 (Ricci, 2019). As high as 80% of those suffering with dementia are diagnosed with Alzheimers, a disease affecting mental agility, language skills, executive functioning and psychomotor skills (Manukhina et al., 2016). This calls for immediate action. As is true with muscle function and respiratory function, brain function also declines with age if strong action is not taken to reduce the vascular risk factors, VRF, that lead to dementia and Alzheimer's Disease (Vaswanathan et al., 2009). The risk of developing these known precursors that lead to the development of dementia and Alzheimer's disease can be lessened through a combination of exercise, voluntary breathing techniques and IHT and IHE (Ferreira et al., 2015; Meng et al., 2020; Serebrovskaya et al., 2019). Not only have each of these been shown in isolation to not only lessen the incidence of VRFs that lead to this severe form of cognitive decline, but can also be used as therapeutic tools post-diagnosis (Max et al., 2017; Serebrovskaya et al., 2019; Zaccaro et al., 2018). Serendipitously, all three aforementioned modalities of exercise, voluntary breathing exercises, and intermittent hypoxia, have all been shown to not only improve respiratory and peripheral muscle function, but also have been shown in isolation and in conjunction with one another to significantly reduce the likelihood of development of the VRFs that are known precursors to the development of cognitive decline (Serebrovskaya et al., 2019).

In the following examination of the mechanisms as to how a breath-induced intermittent hypoxic training program could assist in preventing cognitive decline, the efficacy of each of these methods in isolation and in conjunction with one another is explored in the prevention of cognitive disease. Also, a discussion will ensue on the outstanding potential of the culmination of breath-control, intermittent hypoxia and exercise in enhancing cognition, including short and long-term memory, spatial awareness, reactive capabilities, and posture and balance (Navarrete-Opazo et al., 2017). There have been several studies that show significant correlation between improvements in each of the aforementioned factors and prevention of early cognitive decline (Sengupta et al., 2012) . Performing a daily routine that efficiently combines strengthening of the respiratory muscles, the peripheral musculature and the brain is necessary to avoid cognitive decline. Breath induced intermittent hypoxic training, *BIIHT*, combines aerobic and strength exercise with voluntary breathing exercise, inducing intermittent bouts of hypoxia. A routine such as this has the potential to reduce cognitive decline.

The endothelium is a layer of dynamic cells that separate the blood vessel walls from from the blood and is a regulator of the tone of the vasculature as it exchanges messages between the blood, its cells and the blood vessel wall (Sandoo et al., 2010). Nitric oxide is a gaseous molecule that the endothelium is highly responsive to, and the dysregulation of which can be the precursor for hypertension, diabetes and hypercholesterolemia (Tousoulis et al., 2012). Not only have raised levels of nitric oxide been shown in response to intermittent hypoxia protocols, but also slow breathing protocols, especially when performing nitric oxide enhancing nostril breathing as it stimulates the olfactory bulb to produce this gaseous, disease preventing molecule (Scadding, 2007). An increase in nitric oxide (NO) causes vasodilation of the blood vessels, which is the relaxing of the vessel wall with the subsequent opening of the vessel, reducing blood pressure and increasing delivery of oxygen and nutrients to every cell in the body (Sandoo et al., 2010). Cognitively, brain function has been shown to improve with an improvement in the cerebral vessels' endothelial exchange mechanisms, bringing more blood flow, nutrients, oxygen and activity in many areas of the brain (Manukhina et al., 2016).

The NO that can be generated from IHT and IHE can assist in better endothelial function in the cerebral vascular system, which contributes to improved exchange of metabolites and toxins through the capillary walls, helping to reduce the risk of the classic atherosclerotic stiffening of the endothelial walls that can contribute to the accumulation of amyloid-beta plaques that are precursors for developing Alzheimer's disease (Manukhina et al., 2009). A key precursor to the development of Alzheimer's disease is under perfusion of the cerebral vasculature and accumulation of beta-amyloid plaques, which is accelerated when NO dysfunction is present (Austin & Katusic, 2020). The upregulation of HIF-1 in response to intermittent hypoxia aids in the production of nitric oxide, which assists in vasodilation of the cerebral vessels (Kang et al., 2021). Furthermore, another downstream trophic factor that is upregulated in response to the IH induced HIF-1, VEGF vascular endothelial growth factor, contributes to the angiogenesis or new blood vessel growth in the brain (Satriotomo et al, 2016).

Dysregulation of the production of nitric oxide in the brain is one of the leading causes of under perfusion in the cerebral structures (Manukhina et al., 2016). Under perfusion is a known vascular risk factor (VRF) that can be improved through the regulation of nitric oxide through intermittent hypoxic training (Serebrovskaya et al., 2008). Aerobic exercise and high intensity interval training, have also shown to consistently result in a high level of angiogenesis and reduction of dangerous free radicals due to aerobic exercise's ability to strengthen antioxidant capacity of skeletal muscle fiber (Powers et al., 2020). The combination of intermittent beneficial hypoxia and aerobic exercise, IHT, has consistently shown positive outcomes in terms of brain derived neurotrophic factors (BDNF) and antioxidant enzymes, both of which greatly improve cerebral vascular function, acting as a preventative mechanism for cognitive decline or a therapeutic modality for those suffering with cognitive decline (Satriotomo et al., 2016; Schega et al., 2013; Wilkerson & Mitchell, 2014). Furthermore, high-levels of antioxidant enzymes and neurotrophic factors such as BDNF correlate with daily enhanced cognitive functioning such as short and long-term memory and reactive ability (Weinstein et al., 2014).

Meng et al. (2020) showed that the increased hippocampal levels of BDNF were directly raised in following the IH exposure to their experiment using mice. In addition, the lowered levels of both amyloid-beta plaques and the proteins that cause apoptosis, cell death, were directly related to the IH in the study on transgenic mice. Oxidative stress caused by an excessive amount of reactive oxygen species, ROS, and reactive nitrogen species, RNS, is abundant in the cerebral structures of those suffering from AD (Aslan & Ozben, 2004). A strong antioxidant defense system stimulated by a higher amount of antioxidant enzymes, as is produced from IHT, has the potential to fight oxidative stress in the brain. It was found that there was an increase in SOD, superoxide dismutase, GP, glutathione peroxidase, and CAT, catalase and a reduction in total oxidant actively in a group of encephalopathy patients after a treatment protocol of intermittent hypoxia (El'chaninova et al., 2002). In the hippocampus of adult rats, it was found that there was an increase in neurogenesis and a decrease in depressive behavior in those exposed to intermittent hypoxic cycles, both of which are linked to a prevention or increase in cognitive decline (Zhu et al., 2010 , other cite). Degeneration of the hippocampus is a vascular risk factor that can be avoided with exercise, voluntary breathing, and IHF and IHE, all of which also aid in protecting age-related lung decline and bolster HRV (Ahlskog et al., 2011; Dale et al., 2014; Liu & Nusslock, 2012; Manukhina et al., 2016; Russo et al., 2018).

Tsai et al. (2011) showed in a groundbreaking study that intermittent hypoxia resulted in hippocampus neurogenesis in rats and an increased level of c-fos transcriptional factor, which has been associated with new environment stimulus, experience-based learning, improved memory and spatial learning (Eagle et al., 2016). The authors of this study make the point that the 12% FiO2 that the rats were exposed to for 4 minute exposures has also been shown in other studies to improve memory, spatial awareness and other areas of cognition through the increased vascularity of the hippocampus due to an increased level of BDNF. This study was unique in that through exposure to varying levels of hypoxia with the subsequent rising levels of HIF-1, they were able to isolate the rises in beneficial c-fos with the IH exposure. The authors also make the point that the chosen 12% FiO2 intensity has a beneficial effect, but lower levels such as 5% FiO2 for longer durations have shown deleterious effects such as hippocampal apoptosis (cell death) and oxidative stress that the brain cannot recover from. This is another fine example of Selye's GAS and the importance of finding the optimal minimal effective dosing (Selye, 1950). Not only is neurogenesis of the hippocampus key in preventing and providing therapy to those suffering cognitive decline, but also reducing hippocampal cell apoptosis is a successful mechanism that has been affiliated strongly with intermittent hypoxia regimens (Zhen et al., 2014).

7.2 Intermittent Hypoxia, Somatic Motor Plasticity and Long-Term Facilitation

Intermittent hypoxia has been shown to not only have a high level of efficacy in terms of preventing the cognitive decline that leads to dementia, but also has been studied and is used in clinical settings to increase the motor plasticity in those who have suffered spinal cord injuries injuries (SCI) (Naverrete-Opazo & Mitchell, 2014; Trumbower et al., 2017). Dr. Gordon Mitchell and his team at the McKnight Brain Institute have shown in several studies, and in a clinical setting, that intermittent hypoxia is highly effective at allowing those with SCIs to have “movement windows” that allow them to move parts of their body that they were not able to move before (Fuller & Mitchell, 2017). This gives the patients opportunities to relearn to walk, talk and grip in a therapy session after being exposed to less oxygen because of the increased levels of serotonin that upregulate BDNF, allowing for spinal motor neurons to make connections with the brain that were not previously possible due to their debilitating injury (Hayes et al., 2014). Chistiansen et al. (2021), a colleague of Mitchell’s, confirmed that motor neurons of the hand can be potentiated following an intermittent hypoxia protocol. Additionally, locomotion has been shown to be improved in those with SCI with improved walking speed and endurance following a 3 week protocol (Navarette-Opazo et al., 2016).

Trumbower et al. (2012) presented results of significantly increased plantarflexion at the ankle joint after intermittent hypoxic exposure. The authors make the point that somatic motor neuron plasticity conditioning is a highly feasible and low risk therapy for those with SCI. Dougherty et al. (2018) presented interesting research that indicated that serotonin is involved in the increase in motor activity between the spine and the brain, but that this transition is made when the spinal injury is considered as chronic vs. acute at the 2 week mark. Much more research is needed in this area in terms studying the effects of motor skill learning on a healthy population. If motor neurons are potentiated in those with SCI, how would this potentiation affect an health individual or an athlete in need of a competitive edge? Refer to 5.3 Motor Learning chapter for a deeper exploration on motor learning and IHT.

Long-term facilitation, LTF, is the plasticity of the respiratory system. Many studies have shown that breathing mechanics improve after exposure to intermittent hypoxia. Tester et al. (2014) showed that there was an increase in minute ventilation after a 30 minute intermittent hypoxia protocol. Additionally, it was shown that 5 intermittent hypoxic cycles of 1 minute exposure to 14% FiO2 induced improvements in minute ventilation up to 30 minutes following treatment on rabbits (Sokołowska & Pokorski, 2006) The clinical significance of increasing minute ventilation in a population such as SCI patients, who have a central disconnect with the respiratory system, is significant and could be the difference between living with full functional capacity and suffering the systemic consequences of inadequate respiration, including mortality.

7.3 Recommendations on Application

It has been made clear that there is a strong connection between cognitive enhancement and intermittent hypoxia. The question that arises in the reader's mind is: what is the best method of implementation? Climbing up a mountain or finding a hypoxic chamber is not the most convenient or cost-effective method of application. A method that needs much more research, but is low-risk and worthy of application is voluntary apnea. Voluntary apnea in a low-lung volume state, as Xavier Woorons has shown in an abundance of his research, can bring the SpO2 down to 85% for several seconds at a time while performing high intensity exercise (Woorons et al., 2017). In addition, Dr. Malshe demonstrated intermittent hypoxic exposure with nisshesha rechaka pranayama, inclusive of VA, with subsequent intermittent low SpO2 levels (Malshe, 2011). Dr. Patrick McKeown in his book *The Oxygen Advantage*, born out of the school of the Buteyko method, emphasizes the need to condition the chemoreceptors by increasing their threshold and sensitivity to the build-up of CO2 within the system (Prabhakar & Kline, 2002). Additionally, a pranayamic breath hold on an exhalation is called Bahir-Kumbhaka, and has been shown to not only successfully raise CO2 levels, bringing the SpO2 levels down, but also increases CBF, cerebrospinal fluid, and shows parasympathetic dominance during the voluntary apnea, VA (Nivethetha et al., 2016).

Breath is fundamental to life. Humans can exist without food for a few weeks, without water for a few days, but can only exist without oxygen for a few minutes (Kottusch et al., 2009; Leach & Treacher, 1998). Countless studies have shown that breathing routines that assist in strengthening the respiratory muscles and lungs not only improve heart rate variability that lessen cardiovascular risk factors, but also enhance cognition through improved neurogenesis in key memory areas of the brain such as the hippocampus with coinciding higher resting SpO2 levels, representative of hemoglobin functioning (Budhi et al., 2019; Mason et al., 2013). Additionally, IHE and IHT have been shown to boost SpO2 resting levels in addition to upregulating hippocampal neurogenesis (Hetzler et al., 2009; Manukhina et al., 2016) A reliable recommendation to a patient, who may be at risk for cardiovascular disease with a positive genetic test for the APOE4 gene, is a protocol that utilizes a combination of all methods available to prevent and treat cognitive decline (Montagne et al., 2020).

Aerobic exercise has also been shown through the upregulation of BDNF, a growth factor for new neurons, to increase cerebral perfusion, which enhances cognitive functioning and prevents VRFs that are precursors to the development of dementia and Alzheimers (Manukhina et al., 2016). Combining exercise with breath training and intermittent hypoxia has the potential to not only enhance daily cognition, but also serve as a therapeutic preventative mechanism for the onset of these debilitating disease. *BIIHT* has the ability to cover all 3 components of a program inclusive of each of these areas, but much more research is necessary on this hypothesis as a breath induced protocol for hypoxia has not been adequately researched. IHT within a hypoxic chamber or breathing approximately 15% FiO2 is another method that can accomplish the areas of exercise and intermittent hypoxia (Serebrovska et al., 2016). The implementation of a breath routine, inclusive of slow breathing, forceful exhales, and VAs into a workout can not only strengthen the lungs and respiratory muscles, but also reduce VRFs and improve blood oxygen saturation. This is an area that should be further explored for full realization of potential.

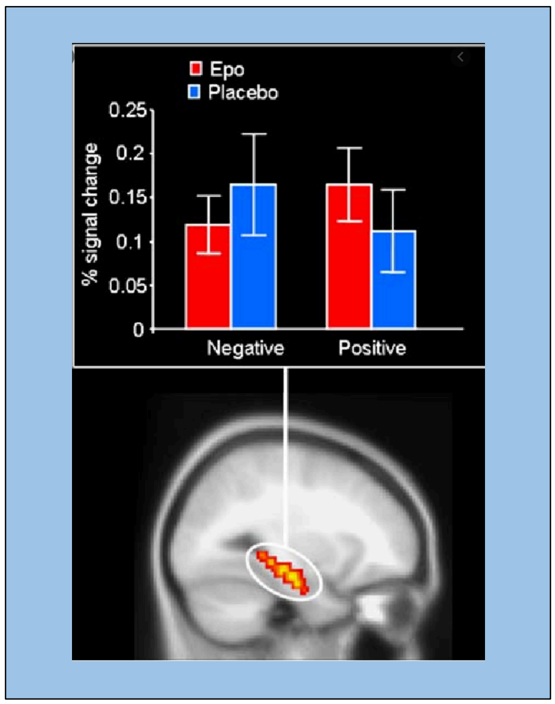
7.4 Cognition & Breath

High stress correlates with disease. Cognitive decline has been directly connected with higher levels of activity in areas of the brain that have been studied as representing anxiety, depression, and fear (Ma, 2020). Furthermore, hyperactivity in areas of the brain such as the amygdala have been observed to not only be links to depression, fear, and anxiety, but also can lead to the oxidative stress that is a risk factor for cognitive decline (Yang et al., 2020). In a study that looked at MRI imaging before and after a one month pranayama training protocol, it was found that there were reductions in activity of the amygdala post training. It was also noted that slow exhalations correlated with increased activity of the parasympathetic nervous system (Novaes et al., 2020). Therefore, implementation of a slow exhalation that is at minimum twice as long as the inhalation could reduce the VRFs of oxidative stress in the brain via the stress lowering mechanism of increasing vagus nerve activity and the parasympathetic nervous system (Gerritsen & Band, 2018). Because six breaths per minute is the suggested rate across the literature because of the clearly delineated evidence connecting this rate with reduction in stress and improved cognition, a tempo of a two seconds inhalation and eight seconds exhalation can be recommended for not only a decrease in stress, including oxidative stress, but also an increase in abdominal strength, respiration strength and lung health (Saoji et al., 2019).

An exercise and breathing protocol that strengthens the respiratory muscles through slow breathing, forceful exhalations and VAs is an effective method of enhancing cognition such as short-term/long-term memory, improved parasympathetic dominance (HRV), spatial awareness, and reactive abilities (Ferreira et al., 2015). Breathing at a controlled rate of 6 breaths/minute has been shown to improve vagal tone and raise HRV scores (Russo et al., 2018). The correlation between cognition and HRV scores are directly linearly related in terms of the onset of cognitive decline (Forte et al., 2019). Slow breathing, as has been studied in pranayama research for decades, has shown an increase in alpha slow waves in the brain vs theta, the latter of which correlates highly with the neural circuitry of those diagnosed with AD (Bhattacharya et al., 2011). Del Negro et al. (2018) makes the connection between improved ventilation such as FRC, FEV, and tidal volume when performing active exhalation. All of these components of healthy respiration are directly related to cognition (Dodd et al., 2015; Suglia et al., 2009). The healthier the lungs, the healthier the mind. Individuals diagnosed with AD have been shown to have a higher than normal RV, residual volume, the amount of air left in the lungs at full exhalation (Dodd et al., 2015; Lofrese et al., 2020). The residual volume can be decreased through proper respiratory strength training (McCartney et al., 2016).

Slow breathing has been shown to increase vasodilation of the brain with subsequent improved endothelial function with associated reduced oxidate stress through upregulation of nitric oxide and superoxide dismutase (SOD), am anti-oxidant free radical scavenger (Patil et al., 2014). Because oxidative stress is a leading VRF in the development of cognitive decline, slow breathing is warranted as a method of prevention (Hajjar et al., 2018). Voluntary apnea (VA) has also been shown to improve the vasodilation of the brain with associated elevated CO2 levels and the subsequent high activity of the chemoreceptors of the brain in response to the low oxygen levels from the VA (Saoji et al., 2019). In addition, it has been shown that the increased activity from the chemoreceptors neurally in response to a breath-retention in pranayama or a free-diver's breath-hold induces plasticity (respiratory) and increased activity in the brain that enhances cognitive function (Gerritsen & Band, 2016; Nivethetha et al., 2017; Nivethetha et al., 2020). OSA sleep apnea is on the other end of the spectrum in terms of oxidative stress and endothelial exchange mechanisms. Instead of boosting the antioxidant pathway, OSA produces a high number of free radicals that the organism cannot recover from and vasoconstricts the cerebral blood vessels instead of vasodilating, which leads to less blood flow and exchange of nutrients (Durban & Bryan, 2012). These severe, chronic doses vs the acute and less severe doses of hypoxia induced by VAs causes negative changes in the brain such as hippocampal apoptosis alongside the aforementioned vasoconstriction (Macey, 2019). Voluntary apnea, VA, has also been shown to increase levels of EPO in response to low levels of oxygen in the system (de Bruijn et al., 2008; Elia et al., 2021). EPO has been shown to not only improve oxygen carrying capacity with a higher level of red blood cells that carry hemoglobin, but it also has been shown to have a protective effect on vital organs such as the heart and the brain (Nguyen et al., 2014). EPO has been shown to stabilize the mitochondrial membrane, reduce reactive oxygen species and reduce the number of pro-inflammatory cytokines in the brain (Villa et al., 2003, Yu et al., 2013). All of these factors that EPO minimizes are VRFs for cognitive decline, inclusive of Alzheimer's Disease (Perry et al., 2002).

Figure 20



Note: Increased EPO levels correlate with improved emotional processing. Adapted from: "Effects of erythropoietin on emotional processing biases in patients with major depression: an exploratory fMRI study.", by Miskowiak, K. W., Favaron, E., Hafizi, S., Inkster, B., Goodwin, G. M., Cowen, P. J., & Harmer, C. J. (2009). *Psychopharmacology*, *207*(1), 133–142. https://doi.org/10.1007/s00213-009-1641-1

7.5 Breath, IH and Depression & Anxiety

Not only have IHT and IHE been shown to increase resting levels of SpO2, a representation of the optimal functionality of hemoglobin, but also respiratory strengthening exercises have had great efficacy in this area (Czuba et al., 2018; Zuriati et al., 2020). With age, normal resting SpO2 levels decline to an average of 94% in contrast to 97% in younger years (cite). 95-100% is considered normal (Vold et al., 2015). With age, hemoglobin capacity is minimized as a result of many factors including physical fitness (Zakai et al., 2013). IHT is an effective protocol for strengthening hemoglobin's affinity for oxygen, which results in a higher SpO2 level (Hamlin et al., 2010; Leone & Lalande, 2017; Naverrete-Opazo & Mitchell, 2014; Yalcin & Cabrales, 2012). Furthermore, respiration exercises that improve FRC, FEV and TLC have been shown to correlate with higher resting SpO2 levels and higher VO2 max levels, which IHT protocols have been effective at raising, much to the delight of the devoted athletic IHT followers (Bilo et al., 2012). Using a combination of slow breathing and forced exhalations as a component of an IHT protocol has the potential to multi-factorially improve hemodynamics (Jung et al., 2020; Laborde et al. 2019; Park et al., 2018). A *BIIHT* protocol could effectively implement all of these components. Because a lower resting SpO2 level and lesser hemoglobin functionality has been shown to correlate with cognitive decline and optimal vitality, a combination of respiration and fitness exercises are warranted as an effective protocol to therapeutically target the symptoms and possibly prevent the onset of cognitive decline (Dodd, 2015).

In the closing remarks about the role of voluntary breathing during exercise and intermittent hypoxia as a cognition enhancer, all three components have a strong place in promoting positive adaptations in the brain structure. Depression is a disorder that has been shown to be reflective of changes in brain structure and metabolism (Zhang et al., 2018). Oxidative stress is not only a precursor for the cognitive decline leading to dementia and AD, but also depression, which affects directly or indirectly every household globally (Gella & Durany, 2009; Lim et al., 2018; Salim, 2014; Petterson et al., 2015). The majority of the world either suffers with or has a loved one who suffers daily with depression and anxiety. In 2020, the global rates of anxiety and depression were up to 35% and were compounded by the Covid-19 pandemic (Salari et al., 2020). Intermittent hypoxia, voluntary breath manipulation and respiration strength training been tied to lessening anxiety and depression (Gerritsen & Band, 2016; Kushwah et al., 2016; Nivethetha et al., 2020; Russo et al., 2017). The usefulness of combining these methods into a protocol that addresses depression and anxiety on a daily basis has the potential to alleviate most households in the world of the negative consequences of episodes of anxiety and depression.

In 2020, a unique perspective on treating depression via manipulation of HIF-1 and the correlating ROS associated with mitochondrial oxygen metabolism in order to alleviate the oxidative stress pre-cursor of major depression was published in *Medical Hypotheses* (Kang et al., 2020). The authors hypothesized that increases in HIF-1 could be a means of regulating the PCr/CK circuits in the brain, which not only serve as a high energy substrate for brain metabolism, but also tend to be on the low side in those diagnosed with major depressive disorder MDD (Harper et al., 2017). Kang and colleagues showed an increase PCr/CK in the epithelium of the intestinal wall after hypoxic exposure with subsequent elevated levels of HIF-1. The results of this research bolster the hypothesis that a combination of intermittent hypoxia and voluntary breathing during exercise can serve a therapeutic for not only the aforementioned anxiety and depression, but also chronic disease and athletic potential (Karhausen et al., 2004). If increased HIF-1 levels lead to a metabolic neural substrate shift with increased amounts of PCr/CK in more extensive research, this could be ground-breaking in the world of depression.

As another method of increased neural PCr/CK levels, high intensity exercise (HIIT) has been shown to decrease the uptake of neural glucose from the resting state and increase the availability of alternative substrates such as lactate and PCr/CK for use, which additionally can raise the resting levels of PCr/CK (Matura et al., 2017). Although upregulation of BDNF and VEGF have been shown as huge factors in the improvement of depressive systems, as these neurotrophic factors are also increased with the pharmacological treatment for depression, the transfer to alternative energy substrates such as PCr/CK with intense exercise is a valid alternative for alleviation of depressive symptoms (Pisoni et al., 2018). Even though HIIT is an effective modality of increasing PCr/CK levels, only a portion of the population is able to work to this high intensity without running the risk of injury; hence, utilizing intermittent hypoxia to increase this high energy substrate in the brain is much more feasible for the majority of the population (Lunt et al., 2014; Rynecki et al., 2019).

HIF-1 is a transcription factor in control of increasing amounts of VEGF, which increases brain angiogenesis, in addition to controlling the pathways of glycolysis, PCr/CK circuit and the lactate shuttle in the brain (Semenza, 2011). If indeed HIF-1 is increased in the brain through IHE and IHT, this could have important implications in need of further research to investigate non-pharmacological alternative strategies for depression. Because oxidative metabolism is decreased when either performing high intensity exercise or IHT/IHE, there is a greater reliance on the glycolytic and PCr/CK system (Kang et al., 2020). The predominance of glycolysis can aid in the reduction of oxidative stress resulting in fewer free radicals because of the downregulation of the use of oxygen with its subsequent reduced forms (ROS and RNS)

(Kondoh et al., 2007). Therefore, an increase in HIF-1 in the tissues of the body would correlate with less oxidative stress, which is a precursor to inflammation, chronic disease, and all-cause mortality (Liguori et al., 2018). It has been shown that levels of HIF-1 increase in the brain after exposure to both IHE and IHT (Merelli et al., 2018; Viscor et al., 2018). In a 2009 review looking at the current research in the world of HIF-1 and the brain, the author cites several examples of exponential increases in HIF-1 as the duration of exposure to hypoxia increased (Bernaudin et al., 2002; Shi, 2009).

Increases in HIF-1 not only correlate with increases in the aforementioned depression-alleviating PCr/CK substrates, but also increase levels of EPO and VEGF, both of which have a neuro-protective effect as they provide neural protection from ischemia or stroke while increasing angiogenesis and cerebral blood flow (Yeh et al., 2011). If indeed intermittent hypoxia has the ability to cause a shift in neural energy substrates that aid in preventing depressive symptoms and increasing the efficacy of pharmacological depression medication, then this opens up a world in which the depressive patient can alternatively manage symptoms with a low-risk, non-pharmacological strategy that does not predispose oneself to the high injury rates of HIIT that is otherwise necessary to achieve dramatic substrate shifts in the brain (Matura et al., 2017). If indeed a breath-induced protocol has the ability, through a combination of slow breathing, forced exhalations and VAs, to increase levels of HIF-1 in the brain, this could not only have a neuroprotective role, but also a cognitive enhancing and a depression management effect through HIF-1's downstream effects (Pisoni et al., 2018).

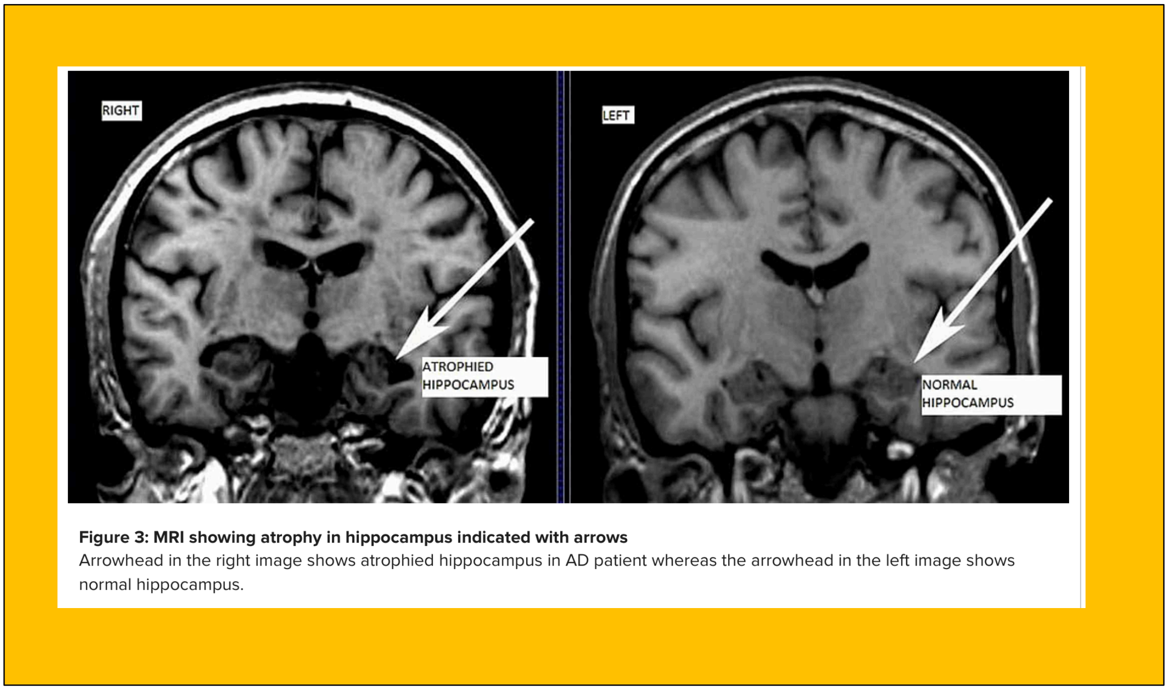
Obstructive Sleep Apnea is a chronic, severe, and maladaptive version of IH (Tahmasian et al., 2016). Many areas of the brain that fall prey to OSA destruction are the same areas that are "stimulated" with an acute; OSA causes hippocampal apoptosis, yet intermittent hypoxia causes hippocampal neurogenesis (Li et al., 2012; Zhu et al., 2010). Again, finding the parallel between HIIT and IHT is important. Would a coach guide an athlete to perform 1 sprint to exhaustion, with only 30 seconds of recovery, for 8 hours per day? OSA represents this kind of extreme coaching session. This immediately puts an organism into the exhaustion phase with no chance for recovery (Selye, 1950). OSA causes apoptosis of the hippocampal cells, inhibiting short and long term memory formation, whereas acute IH enhances the hippocampus with neurogenesis (new cell growth) with the production of HIF-1A produced BDNF, VEGF and EPO (Dale et al., 2014; Yuan et al., 2015). OSA causes free radical production in the brain, which becomes a pre-cursor for AD and all cognitive decline, whereas IH promotes and strengthens the antioxidants pathways that "battle" the free radicals and act as a neural "pre-conditioner" in order to protect the brain from future ischemia (stroke) and reactive oxygen species production (Recuero et al., 2010; Sprick et al., 2019).

The research is plentiful in supporting that increased levels of EPO, BDNF, and VEGF contribute to not only a more successful administration of pharmacological anxiety and depression medication, but also may lay the groundwork for non-pharmacological strategies for prevention of depressive symptoms (Phillips, 2017). Not only has aerobic exercise training been shown to improve levels of these growth factors, but also IHE and IHT have been shown to increase all of these areas that enable an individual with anxiety and depression to manage their symptoms more effectively (Boyne et al., 2020; Dale et al., 2014). In addition to the aforementioned pre-cursors that stimulate growth factors in the brain that increase angiogenesis and new neuron growth that may alleviate and prevent depression, breath control, inclusive of slow breathing and voluntary apneas (VA), has also been shown to upregulate these areas (de Bruijn et al., 2008; Feldman et al., 2003; Satriotomo et al., 2016).

Not only exposure to hypoxia, but also VAs have been shown to produce a significant increase in EPO several hours after implementation, a factor which has been shown to have a protective effect on the brain not only in terms of damage from stroke, but also in prevention and symptom management in those with depression and anxiety (Hou et al., 2014; Osborn et al., 2013). Increased hippocampal neurogenesis has been shown not only to improve cognition in terms of short and long-term memory, but anxiety and depression (Hill et al., 2015). IHT, IHE, aerobic exercise and voluntary breath control have all been shown to increase EPO, BDNF, and VEGF, contributing to a significant increases in neurogenesis in the hippocampus, in addition to many areas of the brain, affecting not only mood, but also reaction and memory (Dale et al., 2014; Ferreira et al., 2015; Zaccaro et al., 2018). Combining all of these methods as a mood stabilizer, injury preventative technique, and cognition enhancer could be an effective tool for every member of society. *BIIHT* is a suggested protocol combining elements of breath control, increased core recruitment, and intermittent doses of acute hypoxia. Much more research is needed to observe the effects of not only the combination of voluntary breathing routines in conjunction with an altered FiO2 either at altitude or in a hypoxic chamber, but also utilizing a *BIIHT* breathing routine independent of an altered environmental FiO2 to induce the beneficial effects of intermittent hypoxia, all the while improving biomechanics and mental health.

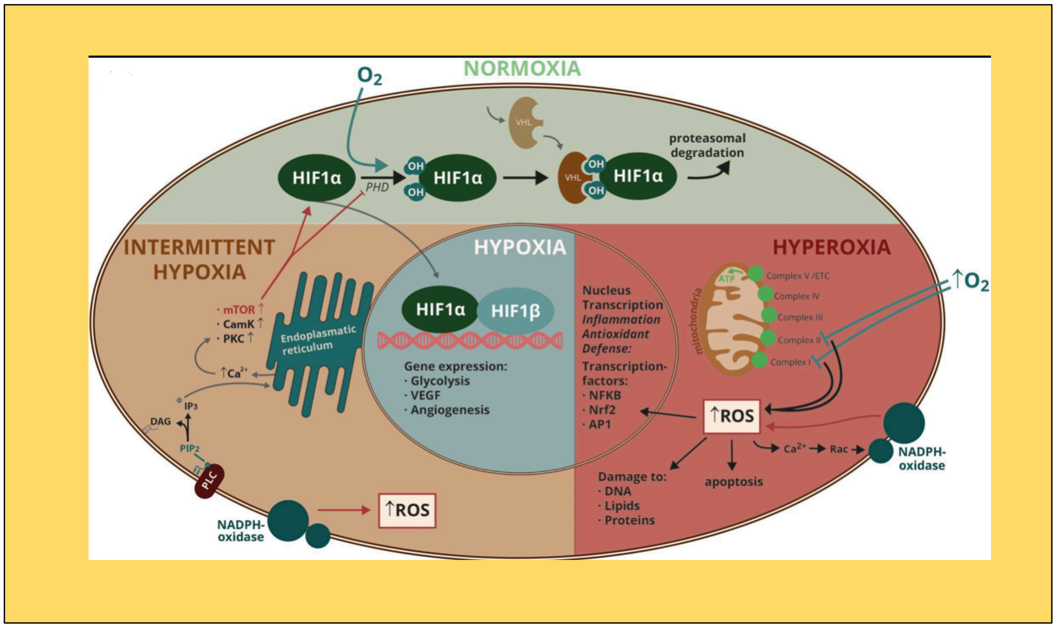
Future investigation is warranted for further examination on this topic. Examining "side effect-free" depression/anxiety treatment strategies inclusive of respiration strength, intermittent hypoxia and exercise could assist in developing effective treatment plans that not only alleviate the suffering of this common mood disorder, but also reduce the comorbidities that coincide (Wu & Fang, 2014).

Figure 21



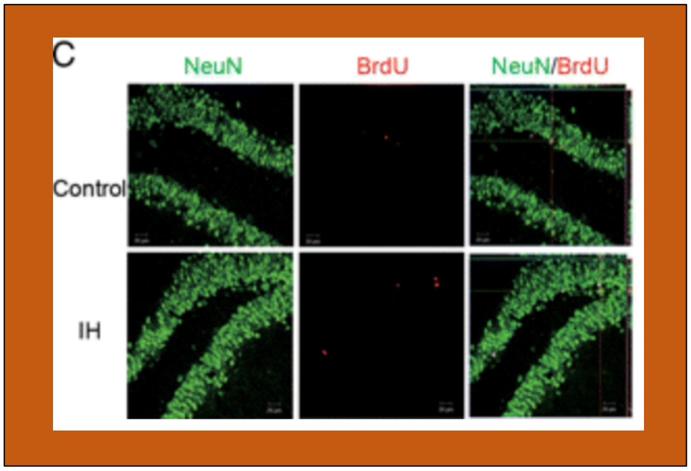
Note: Atrophy of the hippocampus in Alzheimer's Disease patients. Adapted from "The Neuroprotective Effects of Exercise on Cognitive Decline: A Preventive Approach to Alzheimer Disease.", by Rashid, M., Zahid, M., Zain, S., et al. (2020) Cureus 12(2): e6958. doi:10.7759/cureus.6958

Figure 22



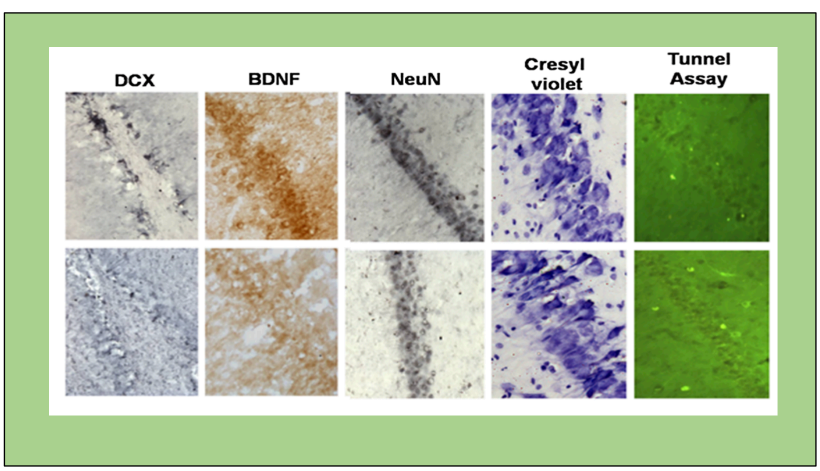
Note: HIF-1 and the downstream factors that are encoded as the brain attempts to achieve homeostasis with too little or too much O2 availability. Adapted from "Investigating Disturbances of Oxygen Homeostasis: From Cellular Mechanisms to the Clinical Practice.", by Tretter, V., Zach, M., Böhme, S., Ullrich, R., Markstaller, K., & Klein, K. (2020). *Frontiers in Physiology*, 11, 947–947. https://doi.org/10.3389/fphys.2020.00947

Figure 23



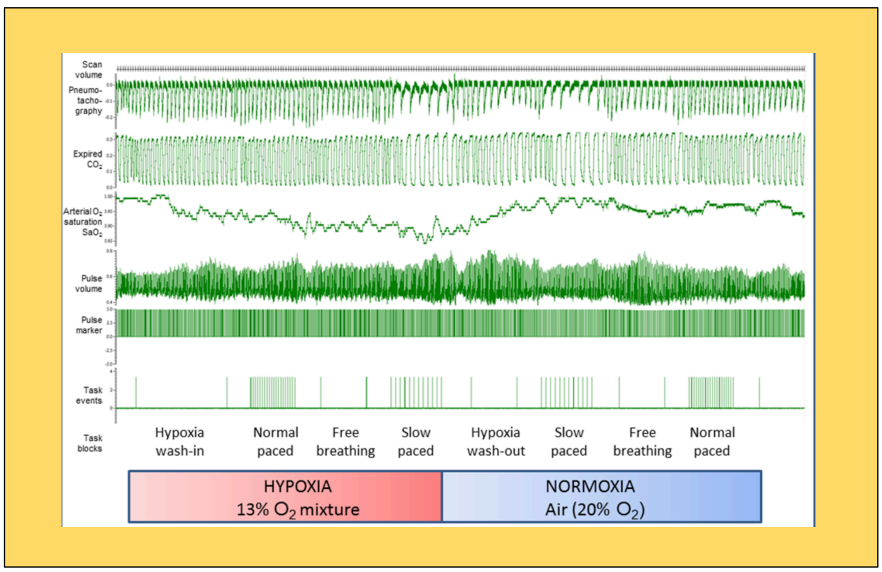
Note: Increased neurogenesis in the adult rat hippocampus after an IH protocol, lessening depressive behavior. Adapted from “Intermittent hypoxia promotes hippocampal neurogenesis and produces antidepressant-like effects in adult rats”, by Zhu, X.H., et al. (2010) *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *30*(38), 12653–12663. https://doi.org/10.1523/JNEUROSCI.6414-09.2010

Figure 24



Note: Increased BDNF, brain derived neurotrophic factor in depressed rats. Adapted from "Neuroprotective Role of Intermittent Hypobaric Hypoxia in Unpredictable Chronic Mild Stress Induced Depression in Rats.", by Kushwah, N., Jain, V., Deep S, Prasad, D., Singh, SB, Khan, N. (2016) PLoS ONE 11(2): e0149309. https://doi.org/10.1371/journal.pone.0149309

Figure 25



Note: Improved HRV, increased brain activity and pulse with hypoxia and slow breathing. Adapted from "Slow Breathing and Hypoxic Challenge: Cardiorespiratory Consequences and Their Central Neural Substrates ", by Critchley HD, Nicotra A, Chiesa PA, Nagai Y, Gray MA, Minati L, et al. (2015). PLoS ONE 10(5): e0127082. https://doi.org/10.1371/journal.pone.0127082

CHAPTER 8

HYPERTENSION

8.1 Hypertension, IHE & IHT

Hypertension is the abnormally high level of arterial blood pressure (Deguire et al., 2019). An alarmingly high statistic of close to 13% of global deaths are related to hypertension (Singh et al., 2017). Clearly, this is an epidemic that affects the majority of the world directly or indirectly. Therefore, there is dire necessity for improving methods of delivery of remedies and preventative mechanisms for the hypertensive individual. IHT and IHE have been shown to be a highly effective method at improving hypertension with applications producing outstanding results, returning blood pressure to normal levels for many months following just one treatment protocol (Serebrovskaya et al., 2016). Nitric oxide is a gaseous signaling molecule produced by the endothelium that assists in proper endothelial functioning, including regulating inflammation (Sharma et al., 2007). Decades of research exists confirming the direct linear correlation between nitric oxide levels and blood pressure that show that nitric oxide, NO, plays a large role in proper maintenance of arterial and endothelial function (Thakali et al., 2006).

Lyamina et al (2011) studied a group of hypertensive patients subjected to an IHE protocol, which resulted in blood pressures brought down to normal for a period of three months following the protocol. The implications of studies such as these that show that brief bouts of hypoxic exposure for a period of four to six weeks with lasting results could have clinically significant implications for the patients and the overburdened health care system resulting in economic devastation due to hypertension, which are at rates as high as $52 billion per year globally

(Wang et al., 2017). Instead of taking a blood pressure medication, which may be higher risk due to side effects than exposing oneself to a low-risk therapeutic dose of hypoxia, a hypertensive patient could have the option of performing just a handful of therapeutic sessions over the course of the year instead of taking daily doses of pills that may tax not only the liver, but all major organs of the body (Serebrovskaya et al., 2016; Serrano, 2014).

Hypoxic treatments for treating hypertension, if inclusive of aerobic and strength exercise in an IHT protocol, offer the additional multi-factorial benefits of effectively strengthening the aerobic and musculoskeletal system (Gangwar et al., 2020). Additionally, the combination of exercise with hypoxic exposure, IHT, has been shown to be more effective than passively experiencing hypoxia, IHE, in terms of nitric oxide production, free radical inhibition via antioxidant pathways, and more significant reductions in both diastolic and systolic blood pressure. Muangritdech et al. (2020) produced statistically significant results that showed that IHT is superior to IHE in terms of levels of HIF-1 and nitric oxide production, both levels of which were doubles in the exercise training, IHT, group. Furthermore, blood pressure reduced and normalized in both IHE and IHT protocols, but the IHT protocols produced approximately 10% improvement over the IHE group. Therefore, IHT and IHE protocols are recommended for the hypertensive patient, but IHT might produce the largest effect in the lowering of blood pressure due to the combination of the NO producing duet, exercise and intermittent hypoxia, and their unique abilities to lower blood pressure through production of this gaseous molecule that governs arterial health (Dyakova et al., 2016). Additionally, inclusion of a structured exercise program provides a plethora of benefits to the hypertensive patient outside of regulating blood pressure, including prevention of all cause mortality from development of comorbidities such as diabetes, cardiovascular disease, obesity and cognitive decline (Tsatsoulis & Fountoulakis, 2006).

The current research on IHT and hypertension suggests that IHT has the ability to compete with currently recommended pharmacological strategies such as beta blockers, ACE inhibitors, diuretics, and calcium channel blockers (Serebrovskaya et al., 2016). The aforementioned study led by Muangritdech (2020) that compared the effects of both IHE and IHT on a group of hypertensive patients, found that not only were HIF-1 and NO levels dramatically higher in those exposed to hypoxic while exercising vs. passively, but also MDA, a compound that is used as a measurement for free radical activity due to it being a byproduct of lipid peroxidation, decreased dramatically, indicating acute activation of both ROS and the coinciding antioxidant pathways that are triggered in response to acute spikes in free radical activity (Gangwar et al., 2020; Meerson et al., 1992). The reduction of the MDA (malondialhyde) compound, that has the ability to be highly destructive to the endothelial lining of an organism's blood vessels resulting in hypertension and cardiovascular disease, is indicative of a successful adaptation to an acute stressor, the hypoxic exposure and exercise, which maintains the organism in the adaptation phase without pushing into the exhaustion phase (Pennathur & Heinecke, 2007; Selye, 1950). If the stressor were applied too strongly with frequencies, intensities, and durations of hypoxia that overwhelmed the organism, these measurements of free radicals have the likelihood of being at the high levels that are deleterious to the body, acting as precursors to the chronic diseases that lead to increased mortality rates (Xu et al., 2004).

Again, the authors of the above mentioned study make note of the fact that the levels of increases in NO and HIF-1 in the IHT groups versus the IHE were more than double, indicating that performing exercise training while exposing oneself to hypoxia is more efficacious at improving and preventing high blood pressure due to the higher amount of nitric oxide that can be generated through the upregulation of the oxygen sensing molecule, HIF-1 (Rodriguez-Miguelez, et al., 2015). Because of the vasodilation that occurs in the blood vessels leading to the muscle during exercise, there is increased blood flow or muscle perfusion and oxygen delivery during IHT in comparison to IHE (Fryer et al., 2019; Núñez-Espinosa et al., 2014). Millet et al. (2016) review the benefits of exercising in hypoxia vs. resting in hypoxia. The authors reinforce that the "compensatory vasodilation" in the blood vessels that occurs as a result of both the raised oxygen demand of the working muscles (VO2 max) and reduced atmospheric oxygen availability results in a double stressor that the body needs to adapt to, hence, producing the aforementioned adaptations that improve hypertension more-so in IHT groups than the IHE (Muangritdech et al., 2020).

It has been shown that those suffering from several chronic diseases, especially hypertension, have a higher than average muscle sympathetic nerve activity, MSNA, which has the ability to not only lead to additional comorbidities, but also mitigates the musculoskeletal system's full functional capacity in terms of mobility, strength and power (de Souza et al., 2013; Esler, 2000). While sympathetic muscle nerve activity must increase and decrease during exercise depending upon intensity, correlating with acute spikes in blood pressure, the sympathetic nervous system should quiet and dampen post-exercise, followed by an increase in parasympathetic nervous system activity contributing to the known low blood pressures of endurance athletes (Dujić et al., 2006; Katayama & Saito, 2019). This is another fine example of the acute stressor being a beneficial, hormetic dose. Acute doses of high sympathetic nerve activity (intense exercise) benefits the organism, but chronic sprinting with no break pushes the organism into the exhaustive phase, represented in this example by a state of chronically dominant sympathetic muscle nerve activity that is present in the hypertensive and the obese (Esler, 2000).

8.2 Voluntary Breathing & Improved Hypertension

Slow breathing, or paced breathing, at six breaths per minute has been confirmed in a countless number of studies to lower blood pressure in groups of hypertensive patients (Nuckowska et al., 2019). Slow breathing at this rate upregulates the parasympathetic nervous system, through an increase in baroreceptor reflex activity, which is activated in the lung tissue through the increased tidal volumes that coincide with slowing down the breathing (Gerritsen et al., 2018; Joseph et al., 2005). The Hering-Breur reflex triggers exhalation, and is activated at the end point of inhalation, when the lungs stretch and signal the baroreceptors lining the lungs (Vadhan & Tadi, 2021). This leads to increases in the parasympathetic nervous system with subsequent vasodilation of the endothelial walls that control blood pressure (Dutschmann et al., 2014; Schwerdtfeger et al., 2020). Ublosakka-Jones et al. (2018) showed in their research on hypertensive patients that slow breathing in combination with inspiratory resistance not only resulted in lower blood pressure, but also increased strength endurance in respiratory and no-respiratory muscles with an increased lung capacity. Cernes & Zimlichman (2017) present a review of the utilization of slow, paced breathing at 6 breaths per minute as a non-pharmacological strategy for the management of hypertension. They make the case that many hypertensive individuals have succeeded in lowering their blood pressure with pace breathing, but they suggest that a breathing protocol called RESPerRATE is used to held guide patients in using a 6 breaths per minute pace. Hypothetically, if more research can support combining a low-risk, voluntary breathing routine with IHT, *BIIHT* has the potential to not only offer the audio breath rate system that RESPeRATE offers, but also visually guide a patient through functional movement training, strengthening the lungs, respiratory muscles, and the plethora of central and peripheral mechanisms from intermittently applying hypoxia (Verges et al., 2015).

While the mechanisms leading to improvements in blood pressure from intermittent hypoxia and slow breathing differ, the end result of vasodilation, which also can lead to improved muscle function and mood, is the same (Bertuglia et al., 2008; Nuckowska et al., 2019). Why, then, combine the two methods for hypertension if both IHT and slow breathing have been shown to produce similar results? The answer to this question is that the combination of the two has the possibility of being even more effective than either method implemented independently with longer lasting results. For example, a study (Critchley et al., 2015) in which the subjects were exposed to 13% inspired oxygen for a long duration, found that the slow breathing at six breaths per minute while being exposed to hypoxia, protected neural and cardiovascular responses to the perceived stressor. The authors found improved heartrate variability (HRV) and increased activity in the cerebellum and mid-brain with decreased activity in the fear/anxiety associated amygdala (Sah, 2017). Therefore, slow breathing while performing IHT could act as a protective mechanism if at any point within the training regimen were the hypoxia to be perceived as overwhelming. Indeed, even though more research is needed in this area, it may be suggested that slow breathing is highly recommended while implementing an IHT or IHE training protocol because of the increased protection and efficacy of combining the methods.

Not only does integrating slow breathing within a hypoxic training protocol act as a strong safety precaution, but it also enhances the vasodilatory affects leading to normalized blood pressures (Cernes & Zimlichman, 2017). Additionally, the anxiety-reducing and abdominal-strengthening benefits of controlled breathing, if the breath regimens are inclusive of forced exhalation, exhalations to low-lung residual volume, and VAs, serve to boost not only healthy blood pressure, but also longevity (Pan et al., 2015; Rantanen et al., 2012). The research that is in dire need of being performed in this area is whether or not a breath-induced intermittent hypoxic training protocol, *BIIHT*, has the legs to stand on to compete with the pharmacological strategies for addressing hypertension. Could a specific choreographed breath routine with periodized prescriptions for intensity, duration, and frequency, inclusive of slow breathing at six breaths per minute, intermittent forced exhalation, and strategic voluntary apneas elicit a training response that goes beyond the benefits of simply breathing slowly? Does lowering a persons SpO2 between 8 to 10 cycles within an IHT routine to a safe dose of 85% SpO2 through slow breathing, forceful exhalations and voluntary apneas, produce enough of a spike in HIF-1 to elicit the increases in NO that lead to not only lowered blood pressures, but also improvements in muscle function and total body and mind relaxation (Núñez-Espinosa et al., 2014)? These questions have the potential to inspire important research study design.

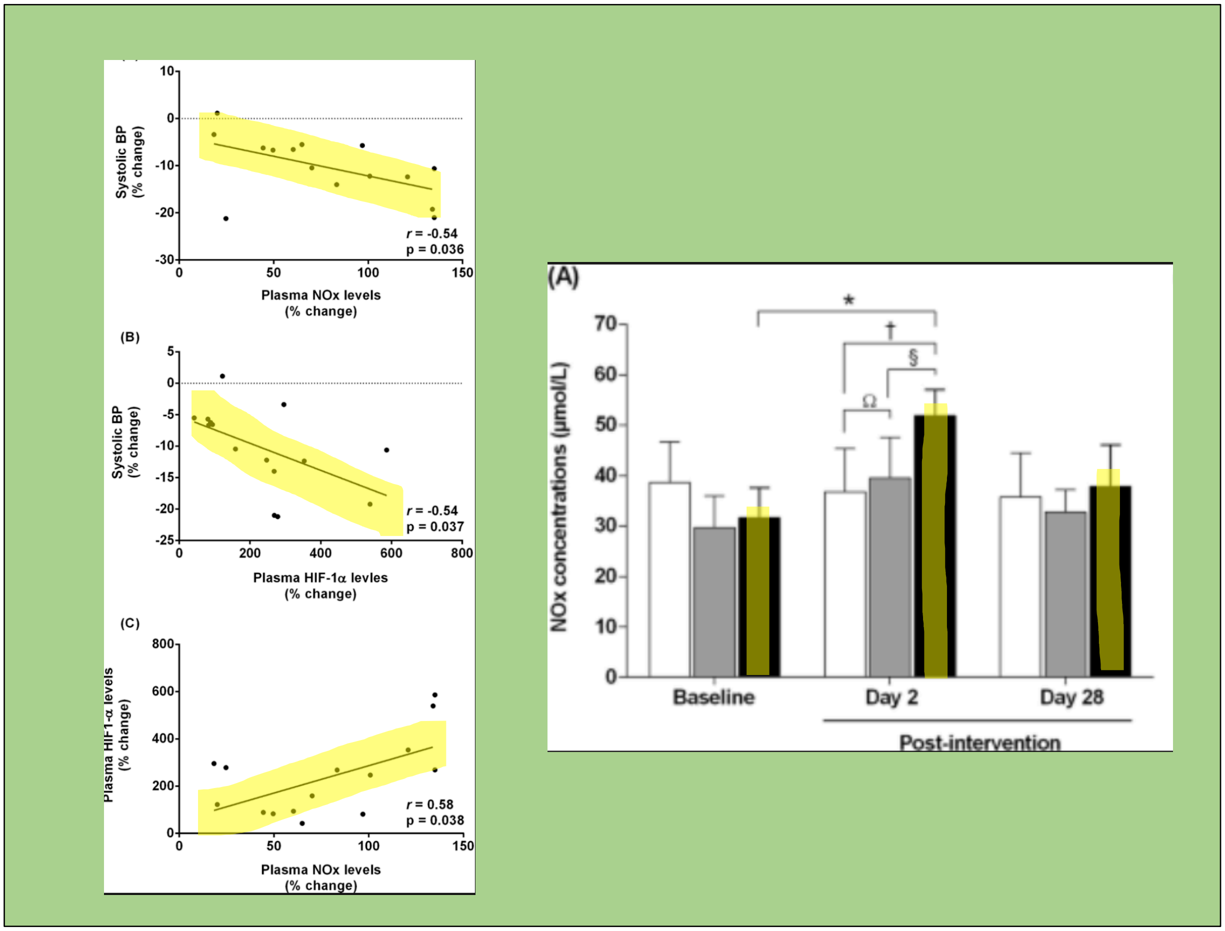
It has been shown that HIF-1, is one of the most quickly degraded proteins after activation (Salceda & Caro , 1997). This is why the highest levels are found when a person is exposed to high altitude for long durations of time (Viscor et al., 2018). That being said, one must to ponder: how much HIF-1 is necessary to achieve a beneficial response? For example, the beneficial durations of the hypoxic dosing for the majority of the motor plasticity response in much of the spinal cord injury research are comprised of intervals as short as 30- 90 seconds (Hayes et al., 2014; Mateika et al., 2015). The measurements of HIF-1 as a result of these short bouts of intense hypoxic exposures for the purposes of regulating serotonin and BDNF to improve motor plasticity and respiratory plasticity for the spinal cord injury patients, is not commonly published, but this is an area that warrants further research. Could it be that producing breath-induced hypoxic intermittent episodes of between 60-90 seconds could produce enough hypoxia inducible factor within the system to engender positive outcomes such as improvements in hypertension?

Interestingly, there has been some unique research in the world of obstructive sleep apnea (OSA) in using mRNA levels of HIF-1 as a method of diagnosing sleep apnea and severity of sleep apnea (Martinez et al., 2019). This research in the world of sleep apnea proves that apneic events while sleeping are enough to elicit a surge in the HIF-1 that would be necessary to potentially induce the vasodilatory protective mechanisms induced by NO in the hypertensive patient. This statement seems like a paradox because obstructive sleep apnea is mostly associated with chronic sympathetic nervous system activation, inflammation, and chronic disease (Bonsignore et al., 2019). Many authors argue that it may be less the intermittent hypoxia that leads to the OSA associated chronic disease, including hypertension, and more the apneic events disrupting regulated sleep cycles (Gottlieb et al., 2009, Sforza et al., 2016). The apneic events during the night intermittently lower oxygen approximately once every 30 seconds all night long, which puts the body in a constant state of sympathetically driven fight or flight for the duration of one's sleep when the body should be resting and digesting in a parasympathetically dominant state (Ferreira et al., 2020). It has been shown that there is a high correlation between sleep disruption and hypertension (Palagini et al., 2013). Additionally, the intensity of the apnea events produced in an individual sleep who is diagnosed with severe OSA tend to correlate with SpO2 levels as low as 60 or 70%, which correlates to an FiO2 of 5%, and altitude levels of above 7000 meters above sea level (Wali et al., 2020). All of these levels are too severe for the organism to adapt to and will push the body quickly into the exhaustion phase of the GAS model, which is represented by the coinciding comorbidities in a person diagnosed severe OSA (Bonsignore et al., 2019).

Is it possible that a breath induced intermittent hypoxic training protocol could mimic the moderate yet effective SpO2 levels of approximately 85%, an FiO2 of approximately 15%, and an altitude of approximately 2500 m above sea level? If these moderate variables could be achieved successfully to produce the adequate levels of HIF-1 that are needed to produce positive results physiologically that help to prevent chronic disease, these breath protocols could be implemented in the convenience of a persons home or training facility alongside their work out. Another interesting measurement to observe would be comparative data between a moderate diagnosis of OSA's involuntary breathing rate, inclusive of apneas, and an exact voluntary breathing replica during the day. If an individual held their breath with subsequent lowering SpO2 levels once every 30 seconds, 60 times per hour, for eight consecutive hours during the day, would this produce the same negative outcomes that the nighttime apneic events produce?

As mentioned in the introduction, stressors such as hypoxic events and apneas can be likened to high intensity interval training. It is generally not recommended to perform more than 60 or 90 minutes of this kind of training per day, with at least 24 to 48 hours of rest in between workouts (Bell et al., 2015). It would be surmised that hypoxic stress from breath-holds would warrant a similar prescription so that the organism can stay in the adaptation phase with proper recovery time, so that oxidative stress levels and subsequent inflammation does not ensue (Khazaei et al., 2012). These are questions that demand answers through much-needed research. As of now, slow, paced breathing is a convenient method for hypertensive patients to perform at home with evidence backed research to prove efficacy (Hering et al., 2013). The most effective training protocol is a combination of voluntary breathing, intermittent hypoxia and exercise. *BIIHT* is further explored in the appendices for the reader's interest. A protocol that dovetails the worlds of slow paced breathing and intermittent hypoxia is supported by the literature for the therapeutic potential of the hypertensive patient.

Figure 26



Note: HIF-1 and NO levels correlate with improvements in systolic blood pressure (BP) in hypertensive subjects after following an IH protocol. Adapted from "Hypoxic training improves blood pressure, nitric oxide and hypoxia-inducible factor-1 alpha in hypertensive patients.", by Muangritdech, N., Hamlin, M. J., Sawanyawisuth, K., Prajumwongs, P., Saengjan, W., Wonnabussapawich, P., Manimmanakorn, N., & Manimmanakorn, A. (2020). *European journal of applied physiology*, *120*(8), 1815–1826. https://doi.org/10.1007/s00421-020-04410-9

CHAPTER 9

CARDIOVASCULAR HEALTH

9.1 Cardiovascular Risk Prevention & Therapy

Cardiovascular disease and intermittent hypoxia has been researched for several decades with a surge in cardiovascular hypoxic research performed in the hypoxic chambers developed for the former Soviet Union's pilots to condition them for flying up to high altitudes (Serebrovska et al., 2016). Both IHC and IHE have been shown to be effective for the improvement and also prevention of the onset of cardiovascular disease as shown in several studies looking at measurements such of homocysteine levels, stroke volume, resting heart rate, myocardial perfusion, blood pressure, blood pressure and HRV (Serebrovska & Shatilo, 2015).

There are several mechanisms by which intermittent hypoxia can potentially improve cardiovascular health. The improvement of sympathovagal tone through upregulation of the parasympathetic nervous system, the lowering of blood pressure through nitric oxide increases, stroke volume, improvement of hematological quality via improved blood viscosity, improvement of the anti-oxidant pathways with reduction in free radicals in the myocardiam, increased hemoglobin and hematocrit through up regulation of EPO and improved ischemia tolerance through ischemic pre-conditioning (Dong et al., 2003; Serebrovska & Shatilo, 2015; Sprick et al., 2019). Beginning with the increases in production of EPO, erythropoietin, in response to hypoxia, the EPO that is produced in the bone marrow, stimulates red blood cell production in the body, improving several components that equate to better heart health such as oxygen saturation through increased oxygen carrying capacity via the increases in hemoglobin in the red blood cells (Cai et al., 2003). Further, EPO has been shown to have a multi-modal mechanisms for protecting the heart that are in addition to the increased oxygen carrying capacity (Navarrete -Opazo & Mitchell, 2014). Cai et al. (2003) showed that their rats injected with EPO were protected from post-ischemic injury, the lack of oxygen that occurs during heart attacks.

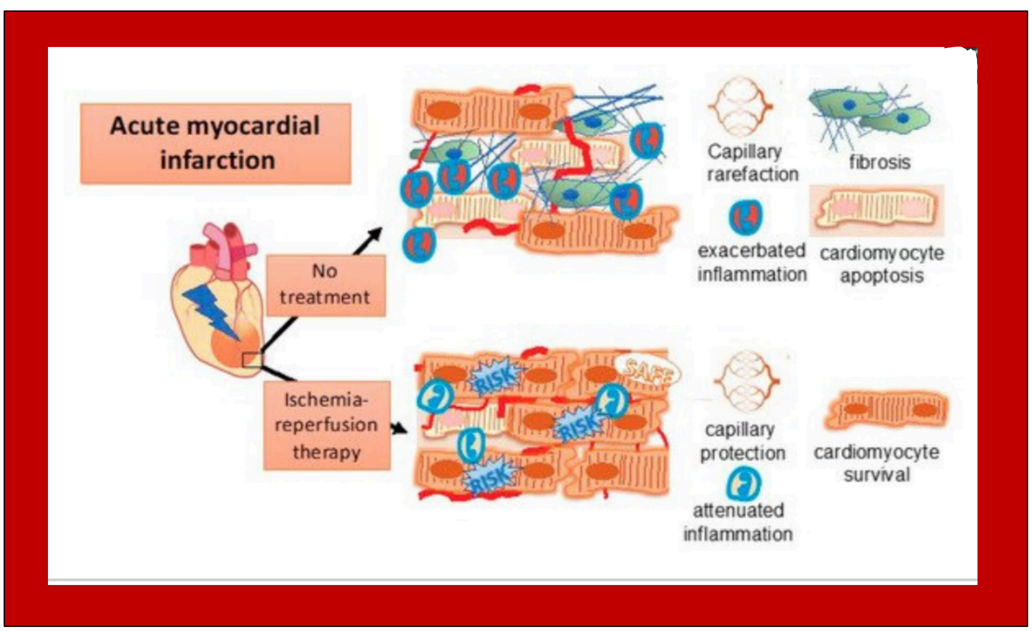
Applying intermittent hypoxia strategically for the protection of the heart from myocardial infarction is called ischaemic pre-conditioning (Stokfisz et al., 2017). Ishcaemic pre-conditioning for the heart acutely applies an ischemia-reperfusion protocol that forces the heart to adapt to this small dose in order to be protected from a "large dose" later on, which is myocardial infarction (Yang et al., 2010). Sprick et al. likened the short, acute doses of depriving the heart of oxygen and then reperfusing it with blood/oxygen to the small, to a hormetic stressor that is highly beneficial when applied in small doses, but detrimental when applied in large doses, as it leads to injury or death. Serebrovska & Shatilo (2015) compare ischemic conditioning, remote ischemic pre-conditioning and intermittent hypoxic training to conclude that IHT has been shown to provide similar effects as pre-conditioning.

Ischemic pre-conditioning works well in theory and in animal laboratory models, but it is possibly dangerous and clinically-challenging to implement (Stokfisz et al., 2017). Ischemic pre-conditioning was originally performed on anesthetized dogs, whose coronary arteries were occluded for 5 minutes at a time for 5 cycles before showing that a subsequent 40 minute occlusion did not cause as much damage to the heart as it otherwise would have without the pre-conditioning (Serebrovska & Shatilo, 2015). A plethora of research has been published on this concept on not only the heart, but other organs such as the kidney and the brain since then. RIPC (remote ischemic pre-conditioning) places a blood pressure cuff remotely on a limb and increases the blood pressure on that area 20 mmHg above resting readings. The limb is held in ischemia for five minutes at a time for 3-4 cycles (Serebrovska & Shatilo, 2015). IHT also reduces the oxygen availability and serves as a form of ischemic pre-conditioning, but without the risks of applying ischemia directly to the heart tissue as it was performed in the premiere research (Meldrum, 1997). Not only does the ischemia response to the IHT induce cardio protection from future heart attack via the upregulation of anti-oxidant defenses in the cardiomyocytes, but also an accumulation of glycogen in oxygen sensitive cells serves a protective mechanism (Mackenzie et al., 2009).

In a recent review article on the therapeutic benefits of intermittent hypoxic conditioning, Mallet et al. (2018) reinforce that while OSA, obstructive sleep apnea causes oxidative stress and chronic disease, acute doses of what the authors call IHC, intermittent hypoxic conditioning, have the ability to reduce the amount of reactive oxygen species in the myocardium through improved anti-oxidants mechanisms. Additionally, the authors emphasize the noteworthy reductions in myocardial infarctions and arrthymias resulting from the IHC alongside increased myocardial perfusion, contributing to improved coronary blood flow. The nitric oxide (NO) increase as a result of the increase in HIF-1, that is upregulated when the body is exposed to hypoxia, not only decreases the risk of hypertension, which is a know cardiovascular risk factor, but also improves HRV through improvements of vagus nerve tone (Viscor et al., 2018). For example, in a group of sedentary individuals, a 4 week IHE protocol resulted in increased vagal outflow with increased HRV scores, indicative if improved cardiovascular health (Lizamore et al., 2016).

The evidence in the literature is strong, yet more research is needed in the world of IHT and IHE and cardiovascular health, especially dissecting feasible protocols that could benefit those with cardiovascular disease who would like effective treatment strategies or those who have had family history or genetic testing to show that they are at risk for CVD and should take every action possible to prevent the onset of cardiovascular disease. Not many have access to the costly and time consuming methods of applying IH for the prevention and treatment of cardiovascular disease such as traveling to a mountain or seeking out a specialist with a hypoxic chamber. The hypoxicator is a smaller, more convenient device, but the cleaning and sanitization of the device is challenging, and the cost can be prohibitive for some. Could a breath induced intermittent training strategy be effective in reducing the risk and preventing CVD? The following section on slow breathing and reduction of cardiovascular risk factors will further explore this inquiry.

Figure 27



Note: Protection of cardiomyocytes from acute myocardial infarction following pre-conditioning IH induces ischemias. Adapted from "Evaluating Novel Targets of Ischemia Reperfusion Injury in Pig Models.", by Baehr, A., Klymiuk, N., & Kupatt, C. (2019). *International Journal of Molecular Sciences*, 20(19), 4749 https://doi.org/10.3390/ijms20194749

9.2 Heart Rate Variability Increases with Breath and Intermittent Hypoxia

A low HRV, indicative of an imbalance between the parasympathetic and sympathetic nervous systems is highly correlative with a high risk for cardiovascular disease. HRV is influenced by the daily energy demands on the body, and a low score correlates with a sympathetic nervous system dominance (Saito et al., 2017). The body is stuck in a chronic fight or flight state, overridden with vasoconstriction and psychological stress, that is induced from a constant load on the body due to the body never becoming "released" from the demands of the environment. This could be due to lack of sleep or meditation, too much exercise, and too much psychological stress, all of which are precursors for not only low HRV scores, but also comorbidities (Kemp et al., 2012; Tyagi & Cohen, 2016).

A communities study that followed almost 10,000 individuals, showed that those who had low HRV scores were more likely than those who had high HRV scores to develop cardiovascular disease at some point in their life (Kubota et al., 2017). Galvanic skin resistance, GSR, is a method of measuring the activity of the sympathetic and parasympathetic nervous system, using two electrodes on skin and measuring the electrical conductivity between the two electrodes. In a study that measured GSR for seven days on a group of meditators performing slow pranayamic breathing and compared this group to the control groups of meditators without performing pranayamic breathing, the authors found that the GSR measurement indicated an increase in heart rate variability in the slow breathing pranayama meditation group (Telles et al., 2013). This study implies that meditation alone may not be enough to elicit a positive change in heart rate variability, but that slow paced breathing is more efficacious.

The slow breathing of various styles of pranayama have been shown to increase the baroreflex sensitivity, which send signals for vasodilation of the blood vessels (Subramanian et al., 2019). High baroreflex sensitivity correlates with high HRV scores and less cardiovascular risk factors, leading to the most optimal cardiovascular health (Joseph et al., 2005). In a review of various styles of breathing, it was noted that breath-retention decreases sympathetic nervous system activity and increase in vagal tone (Nivethetha et al., 2016). If breath holds, slow breathing, and forced exhalations, as is shown in the literature to correlate with high parasympathetic dominance, combine to make exercise more effective and enjoyable, this method of *BIIHT* could be warranted as a mechanism for reducing the risk of cardiovascular disease (Santak et al., 1994). Bernardi et al. (2001) showed that not only did slow breathing exercises reduce the sensitivity of chemoreflex to hypercapnia and hypoxia, but it also enhanced the baroreflex sensitivity. The chemoreflexes are receptors located in the carotid bodies that respond to hypoxemia (low blood oxygen) and in the carotid bodies that respond to hypercapnia (elevated CO2 levels) (Smith et al., 2015). Those suffering hypertension, obesity, and OSA also suffer with high sensitivity in their chemoreflex, which correlates with sympathetic nervous system activation each time there is a slight shift in blood oxygen and carbon dioxide (Kara et al., 2003).

The implications of a low chemoreflex sensitivity is that this person is constantly triggered to be in the fight or flight state, which lays the groundwork for a low HRV score alongside the comorbidities that arise in conjunction (Nivethetha et al., 2016). Practicing a slow breathing technique in conjunction with IHT or IHE is the perfect recipe for improving baroreflex sensitivity, chemoreceptor thresholds and heightening the HRV score (Gerritsen et al., 2018). Again, as mentioned in the previous section, it may become a standard of care protocol to highly suggest, if not require, that an individual practicing intermittent hypoxia executes a slow breathing protocol while performing IHE or IHT in order to improve the chemoreceptor response to the hypoxic exposure, especially as the body is adapting to the protocol. Performing slow breathing while exposing oneself to hypoxia will not only potentially increase the efficacy of heart-protective NO and EPO production, but will also condition one's physiology to be as parasympathetically dominant while being exposed to hypoxia (Lee et al., 2019; Manukhina et al., 2006).

A breath induced intermittent hypoxic training is inclusive of all of the components that have been shown to lower HRV scores, in addition to intermittently inducing hypoxia throughout the breathing session. Much more research is needed to deduce if indeed a method such as *BIIHT* could reduce the risk of cardiovascular disease due to the implementation of a research driven recipe of slow breathing, forced exhalation, and VAs. If the intermittent hypoxic episodes utilizing a choreographed breathing technique could cause enough of a spike in HIF-1 to produce the heart-protective EPO necessary to elicit the positive outcomes for cardiovascular disease risk reduction, the number one global cause of mortality has the potential to be addressed more effectively with a therapeutic, anti-aging, and non-pharmacological strategy (Roth et al., 2017).

Chapter 10 – OBESITY

10.1 Obesity and Breathing Mechanics

Obese individuals tend to have higher ventilation rate: Obesity has been shown to be a predisposing factor in developing breathing disorders such as COPD, asthma, pulmonary hypertension, and obesity hypoventilation syndrome (Peters, 2018) Higher ventilation rates (minute ventilation) make up for the shallow breathing due to impaired breathing mechanics such as fat deposits viscerally and subcutaneously in the trunk region (Pakhale et al., 2015) . In addition, the diaphragm cannot work to full capacity because of these fatty restrictions (Sugarmen et al., 1997). Not only does impaired breathing lead to increased pro-inflammatory cytokines in the system, leading to comorbidities, but it can also lead to obstructive sleep apnea, cancer, suppression of the immune system and higher rates of respiratory infections due to decreased clearance of mucous and debris from the lungs (Poulain et al., 2006; Pirola & Ferraz, 2017).

Components of healthy respiration such as FRC, ERV, FEV and FVC are lower in the obese population and can lead to a weakened immune system with a lesser ability to ventilate without fatigue an exercise routine and clear debris in the lungs that can lead to chronic inflammation and lung disease (Devine, 2008).

Weight loss can improve lung mechanics through the lessening of fatty infiltration at the visceral and subcutaneous level, although it has been shown that the genetic nature of obesity causes this to be an issue that some battle with their whole life (Pakhale et al., 2015; Thacker, 2017). For some, who struggle with this disease for decades, another method of improving respiration may be deemed a necessity to prevent the onset of lung disease and immuno-suppressed mediated comorbidities. Exercising the respiration muscles through a voluntary, breath routine in conjunction with a sub-maximal exercise routine has the ability to not only reduce the risk of chronic disease through becoming aerobically fit, but also increases the strength of the components of healthy respiration that bring forth health and vitality. Acute doses of intermittent hypoxia have been shown in a multitude of studies to reduce levels of body fat and associated comorbities such as hypertension, cardiovascular disease, and type 2 diabetes (T2D), which will be discussed further in the following section (Cardeneso one; Netzer; Serebrovskaya) Therefore, implementing a breathing routine that effectively improves the strength of respiration, increases functional capacity through physical fitness and strategically doses intermittent hypoxia through the breath could have profound implications for the obese.

Increasing heart rate variability has the potential to improve several markers that contribute to obesity at a genetic level. Heartrate variabialit has been shown to be correlated with obesity and so one must ponder the connection between heartrate variability, intermittent hypoxia and obesity.

10.2 Slow Breathing, Gut Hormones, and HRV

HRV and neuropeptide Y. Neuropeptide Y is an orexigenic peptide found in the brain that assists in regulation of appetite (Beck et al., 2006). Neuropeptide Y has been found to be dysregulated in the obese population (Kuo et al., 2007). Kuo et al. showed that neuropeptide Y has been studied in its relation to obesity, showing that there is a high correlation between the dysregulated levels of neuropeptide Y and food cravings. A regiment of intermittent hypoxia that successfully regulates HRV has the potential to improve levels of neuropeptide

Y, which would have a profound impact on a person's food behavior. Using *BIIHT* has the potential to be a highly effective method of inducing hypoxia as they slowed breathing rate of < 6 breaths per minute strengthens vagal tone, improving HRV with a parasympathetic dominance (Russo et al., 2017).

HRV and leptin/ghrelin (I think put this section with the above) – It has been shown that leptin levels and HRV have a relationship. In a cohort study on a police force, researchers found that HRV was inversely related to leptin levels with statistical significance with the police officers with a higher body composition having much higher leptin levels with lower HRV (Charles et al., 2015). Leptin resistance is a known problem in the world of obesity and sympathetic dominance has a high correlation with the obese population, and it has been proposed that "high sympathetic tone" in the obese could be a key factor in the pathogenesis of the disease (Izquierdo et al., 2019; Guarino et al., 2017). Improving parasympathetic tone though not only the breathing mechanisms that upregulate the vagus nerve, but also the subsequent intermittent hypoxia could have the multi-pronged effect of improving the disease (Russo et al., 2017). The overweight and obese are known to have low circulating levels of ghrelin, the orexigenic hunger hormone (Guarino et al., 2017). An interesting study showed that ghrelin stimulates the parasympathetic nervous system, which in turn, increased HRV levels (Soeki et al., 2014; Huda et al., 2010). Another study on the gut biome of individuals at altitude showed that ghrelin levels are lowered at altitude, contributing to the anorexigenic effect that contribute to a person's weight loss when at altitude (Debevec, 2017). The relationship between ghrelin, HRV and obesity needs to be further clarified, but the clear relationships inspire future research on using a combination of breathing, hypoxia and exercise to improve obesity via hunger hormones.

10.3 Slow Breathing, HRV, & Blood Glucose/Insulin sensitivity

High blood glucose is a common trait within the obese population (Akter et al., 2017). Not only does high blood glucose lead to insulin resistance, metabolic syndrome and type 2 diabetes, but it also predisposes a person to fluctuating levels of blood glucose that can wreak havoc on not only the nervous system such as neuropathies, but also the circulatory system and the digestive system in terms of artheroscleroris and the unstable energy levels associated with blood sugar swings (Poznyack et al., 2020). Not only has a low HRV been correlated with high fasting blood sugar, but also this low HRV is a key factor in some of the cardiovascular morbidities associated with the chronic high blood sugar in T2D (Benichou et al., 2018). It has been postulated that the high sympathetic tone of the kidneys and musculature of an individual that leads to vasoconstriction of the muscles, preventing effective glucose uptake, can lead to high blood sugar (Esler et al., 2001). Therefore, integration of slow, voluntary, daily breath-work could, in effect, not only strengthen the vagus nerve, but also cause a reduction in blood sugar due to the decrease in sympathetically driven vasoconstriction of the muscle.

In addition, intermittent hypoxia exposure and training has been shown in several instances to not only reduce blood sugar through high levels of the associated HIF-1, but also improve insulin sensitivity, even though varying results have been seen with severe, chronic exposure as would be experienced in OSA (Serebrovskaya et al., 2017; Thomas et al., 2017). Serebrovskaya and colleagues (2017) found that the blood glucose was lowered in their pre-diabetic cohort for 1 month after the hypoxic exposure with the lowest levels at one month following the treatment. If a breath induced protocol for intermittent hypoxia has the ability to mimic the acute falls of SpO2 that a session such as Serebrovskaya implemented during exercise, this could be a convenient and low cost method of implementing an intermittent hypoxia program. In addition, the likelihood of injury lessens within a workout through increased recruitment of core musculature (Bliven & Anderson, 2013). Reduction of injury enables the diabetic patient to maintain a level of consistency in order to gain strength and muscle mass, which can lower blood glucose via the upregulated GLUT 4 transporter bringing glucose into the muscle cell from the blood (Holten et al., 2004).

10.4 Slow Breathing, HRV, & Inflammation in Obesity

Cooper et al. (2015) presents convincing evidence that HRV is inversely associated with levels of inflammation within the body. The inflammatory macrophages within the high amount of adipose tissue in the obese population are a huge source of inflammation (Lauterbach & Wunderlich, 2017). While reducing the levels of inflammation in the obese phenotype is a certain mechanism to less the risk of all-cause morbidity, preventing inflammation levels in the first place could be a potential method to prevent obesity (Fuhrman et al., 2019). High levels of inflammation within the body are a definitive precursor to type 2 diabetes, which is a known contributor to the obesity epidemic (Pirola & Ferraz, 2017). Improving HRV though a combination of breath-training, intermittent hypoxia and exercise has the ability to lower levels of inflammation and improve body composition.

To wrap up the slow breathing connection with improving HRV and obesity, let the reader be made aware that intermittent hypoxic exposure and training has also been shown to improve HRV and hypoxia can be induced with slow breathing and voluntary apneas (Lizamore & Hamlin, 2017; Park et al., 2018). Although, let the reader note that a lowering of HRV has been observed in the OSA (obstructive sleep apnea population) with an increased sympathetic tone, therefore, dosing needs to be further elucidated (Li et al., 2021).Whether this is correlation or causation is still to be determined and further researched. Establishing connections between slow breathing, increasing HRV improvements, improving obesity and exposure to intermittent hypoxia are worthy of future research.

Weight loss improves HRV, which in turn lessens a person's risk for chronic disease (Sjoberg et al., 2010). An improved HRV has the potential to reduce the risk that a person suffers with obesity in the first place. The two-way relationship of HRV and obesity can be addressed with a combination of breathing, exercise and intermittent hypoxia with *BIIHT*. Not only is *BIIHT* a low-risk tool, but it is convenient and not costly. Much more research is necessary to confirm efficacy, but the benefits, at this point, outweigh the risks and can be recommended to an obese client or patient.

10.5 Slow Breathing, Increased Immunity, and Forced Exhalations

Increased immunity with forced exhalations maneuvers due to decrease debris and inflammation in the lungs: The Forced Expiratory Technique (FET) and Active Cycle of Breathing Technique (ACBT) are both techniques taught by respiratory therapists that strengthens the coughing respiratory muscles, including the abdominals, that assists in clearing debris and sections that could otherwise lead to infection (Fink, 2007). Both FET and ACBT work on utilizing the strength of all of the respiratory muscles to better lung health and condition all of the breathing muscles with a focus on forced exhalation. Integrating a forced exhalation into an obese person's exercise program has therapeutic potential in terms of preventing chronic lung disease and keeping the abdominal/respiratory muscles strong (Ishida et al., 2017).

Forced exhalations to low lung volume with a subsequent breath retention at full exhale at residual volume have the ability to produce intermittent hypoxia more effectively than does breath retention on an inhalation with full lungs. Because in the latter there is more oxygen in the lungs to diffuse into the bloodstream, it takes longer for the SpO2 level to lower down to a place where CO2 levels begin to rise in the blood as is evidenced in voluntary apneas on exhalations or involuntary apneas in sleep apnea (Chang et al., 2014; Dewan et al., 2015). A breathing method integrated within a workout routine, inclusive of a forced exhalation that strategically integrates intermittent hypoxia at the right dose, has the potential to not only increase longevity through the beneficial doses of hypoxia, but also through the strength of the respiratory muscles.

There is evidence to show that the obese population face a challenge in terms of adherence to an exercise regimen (Alberta et al., 2019). With dropout rates as high as 75%, this is an area that needs dire help (Habziabdic et al., 2014). Integration of a forceful exhalation, that has been shown to have a high level of internal/external oblique and transversus abdominis recruitment, into an obese person exercise routine can assist in the prevention of injury (Ito et al., 2016). The obese have a higher likelihood of injury due to increased torque, compression and shear on the joints in addition to higher levels of pain related to pro-inflammatory molecules triggered by adipose tissue and macrophages (Chen et al., 2020; Schmidt et al., 2017).

Because a forced exhalation has not only been shown to decrease levels of low back pain when performed in conjunction with core training exercises in comparison to those who performed the same core exercises without the forced exhalation, but also when combined with slowing down the breath accompanied by a breath-hold for a duration of 1-10 seconds, a strategic lowering of the SpO2 can be achieved intermittently throughout the work out to potentially enjoy the benefits of intermittent hypoxic training (Woorons et al., 2014). The forced exhalation brings the level of air in the lungs down to residual volume, which has been shown to be a more successful strategy in dropping blood oxygen levels (Woorons et al., 2017). Performing an abdominal draw in maneuver, ADIM, while exhaling mimics Zen Tanden breathing, an ancient yoga pranayama whose application has the potential to significantly strengthen the abdominals (Ishida et al., 2012; Zaccaro et al., 2018). An obese individual may find it challenging to do typical core exercises because of the subcutaneous abdominal fat limiting range of motion, therefore, beginning a first phase of a program with sitting and standing breathing exercises that not only strengthen the abdominals and the respiratory muscles, but also improve dominance of the parasympathetic nervous system, could be key in injury prevention and long-term retention of an exercise program for the obese (Boyle et al., 2010; Russo et al., 2017) .

10.6 Fat-loss, Voluntary Breathing, & Intermittent Hypoxia

Increasing the rate of lipolysis, or a fat breakdown is a method of losing more body fat (Duncan et al., 2007). A hallmark of obesity is the slowed down rate of catecholamine stimulated lipolysis in addition to lower levels of hormone sensitive lipase (Arner, 1999). In studies on obesity and IHT, catecholamines have been found at a higher level post-treatment in comparison to the control group, which triggered an increased rate of lipolysis

(Urdampilleta et al., 2011; Workman & Basset, 2012). Combining hypoxia with training methods increases effectiveness and efficiency for the obese. Furthermore, the increased basal metabolic rate, BMR, due to the lesser available oxygen, and using a less energy efficient glycolytic vs oxidative metabolism due to the lower production of ATP, assists in greater intra and post-exercise energy expenditure (Camacho-Cardenosa et al., 2018). This leads to greater weight and fat loss over time in comparison to the same groups performing the same exercise not exposed to hypoxia (Netzer, year).

While the research is noting positive outcomes for the obese population, the hurdle that stands in the way for most is the method of application. Hypoxic chambers and tents are not easily accessible or inexpensive, a trip up a mountain is not time-friendly for most, and training masks can simulate feelings of claustrophobia, in addition to having been shown much less effective than the former modalities (Porcari et al., 2016). The therapeutic potential of a convenient and low cost breathing method that could offer even a fraction of the benefits that have been shown in IHE and IHT in the world of obesity research is grand. *BIIT* has the ability to be conveniently integrated into a home routine is time efficient, not costly and doesn't take up any space in a person's home.

10.7 Injury, Voluntary Breathing, & Intermittent Hypoxia

A plethora of research has brought to light that there is an increased amount of torque, compression and impact in the joints that correlates with bodyweight (Shang et al., 2017). The load on joint increases at an exponential rate the higher the impact the activity (Sandmeier, 2000). In fact, knee osteoarthritis is more prevalent in the obese population due to increased compressive loads on the cartilage (King et al., 2013). One of the most effective methods of decreasing bodyweight aside from diet is performing HIIT in order to increase muscle mass and decrease body-fat (Boutcher, 2010). Not only does HIIT assist in increased post-workout burn, increased blood glucose tolerance, improved glycogen capacity and improved insulin sensitivity, but it also increases the rate of lipolysis through the catecholamines that are generated within a high intensity workout (Zhang et al., 2017). An obese individual direly needs a method of acutely increasing catecholamines periodically in order to reap the benefits of the stubborn subcutaneous fat-loss that is associated with this disease. Unfortunately for most overweight and obsese, HIIT is not possible because of the biomechanical demands (Rynecki et al., 2019). IHE and IHT have been shown to increase the level of catecholamines to a significant level in obesity research, contributing to greater post exercise lipolysis (Urdamilleta et al., 2012). Because the “high intensity interval training energy system”, the glycolytic system, is being utilized when exercising in hypoxia, the body is able to adapt to the exercise as if it had been performing anaerobic glycolysis, even if the exerciser would otherwise be performing low intensity, sub-maximal exercise in normoxia (Camacho-Cardenosa et al., 2018; Ziemann et al., 2011). Having the ability to work at a higher intensity without the strain on the overweight skeleton is profoundly beneficial on many levels. The individual experiences less pain with more enjoyment of the workout, while increasing the effectiveness of the workout and possibly reducing the training plateaus that come along with performing at the same intensity and similar movement patterns for long periods of time (Lorenz & Morrison, 2015).

In addition, HDL/LDL total cholesterol levels have shown improvements after a period of IHT training, which are classically dysregulated in the obese population (Boudewijn et al., 2013; Serebrovskaya, 2016). Zhigang et al. (2018) showed that there was an increase in serum irisin levels and a loss in weight in obese rats, which has the potential to explore another avenue in targeting obesity using IHE and IHT. In summary, there are many potential mechanisms through which IHT and IHE can work to target the obesity epidemic. The main barriers are cost and time efficiency and expense. *BIIHT* has the potential to resolve these barriers if it can be applied in an effective manner within a sub-maximal exercise routine that is not compressive on the joints. Much more research needs to be done to disentangle the holes in the research regarding breath induced intermittent hypoxic training, but it is worthy of exploration.

CHAPTER 11

OSTEOPOROSIS

11.1 Bone Metabolism, IHT, and IHE

Although the area of intermittent hypoxia and bone mineral density is less studied then the decades of research on athletic performance and other chronic diseases, contemporary research has produced results in human and rat studies that present a hopeful envisage in a world where global rates of osteoporosis are crossing 200 million with almost $14 billion in healthcare expenses in the US alone due to osteoporosis related fractures (Akkawi & Zmerly, 2018). Osteoporosis is a skeletal disease in which bone resorption outpaces bone remodeling (Porter & Varacallo, 2020) The highest rates of osteoporosis afflicts postmenopausal women due to lack of estrogen production from the ovaries, and there is a 70% rate diagnosis in those of both sexes over 80 years old (Porter & Varacallo, 2020; Watts, 2018). The pharmacological treatments of biphosphonates, estrogen, parathyroid hormone, and estrogen receptor modulators, have been shown to be effective but not without side effects (Chen et al., 2019).

A non-pharmacological, low risk potential treatment strategy that has shown improved bone mineral density in several studies over the past couple of decades is intermittent hypoxic exposure (IHE) and intermittent hypoxic training (IHT), both of which have been shown to be effective in both rats and humans (Camacho-Cardenosa et al., 2019). The mechanism as to how intermittent hypoxia improves bone density begins with the upregulation of the transcription factor HIF-1 that travels into the nucleus of the cell in order to activate genes that occur when oxygen is low (Ziello et al., 2017). VEGF, vascular endothelial growth factor, and NO are produced as a result of the HIF-1 mediated gene transcriptions, which contribute to angiogenesis and remodeling of bone (Weiss et al., 2000). In fact, it has been shown that the remodeling of bone after a bone fracture utilizes this same mechanism of HIF-1 induced VEGF and NO production, and that exposure to hypoxia accelerates these factors to more effectively remodel the bone (Komatsu & Hadjiargyrou, 2004; Oishi et al., 2016; Zhang et al., 2020).

A moderate dose of hypoxia for 5 hour/day and 5 days/week was applied to a group of rats for 5 weeks, after which the rats showed significantly increased bone mineral density, BMD (Guner et al., 2013). Additionally, Martínez-Guardado et al. (2019) found that an intense resistance circuit training protocol performed twice per week for 8 weeks not only resulted in greater lean body mass, but also greater bone mineral density. The control performed the same exercise in normoxia without significant changes in these areas. It has been found that the joint immobilization-associated muscle atrophy and bone loss post-injury can be lessened if not prevented with exposure to IHT (Bromer et al., 2021). Peng et al. (2014) showed that ovariectomized (surgical removal of ovaries) mice did not experience the typical bone loss that a post-menopausal women experiences after their ovaries stop producing estrogen based on the application of a hypoxia mimicking drug, dimethlyoxalylglycine as it stimulated angiogenesis and osteogenesis in the bone from the HIF-1 transcription of VEGF. Qiao et al. (2018) found that a treatment of IHT, 5 cycles of 12% FiO2 5 minutes at a time for 28 days, resulted in better bone formation and improved healing in comparison to a remote ischemic preconditioning group. There may be a paucity of research, but the research that exists is hopeful in the area of osteoporosis. Bone metabolism and intermittent hypoxia require more scientific attention as this incredibly promising partnership could benefit those suffering from osteoporosis or would like accelerated healing of a bone fracture.

11.2 Bone Metabolism & OSA

Dosing of hypoxia that is chronic with high intensity, as is seen in OSA, can be maladaptive instead of beneficial for the organism, which could lead to bone loss instead of bone formation (Lekvijittada Kochakorn et al., 2021). The systemic inflammation and excessive reactive oxygen species that develop at extreme high altitudes can not only lead to muscle wasting that has the ability to decrease bone mineral density, but also to increases in pro-inflammatory cytokines and subsequent decreases of type one collagen that could lead to a reduction in bone formation (Song et al., 2016). Selye's exhaustion phase is entered when a person is exposed to chronically severe high altitudes for long durations (San et al., 2015; Selye, 1950).

In seeming contradiction to the above statements, one would think that the inflammation that stems from OSA and the acute, chronic, and severe intermittent hypoxia that is endured each night would always lead to a reduction in bone mineral density, but several studies have shown that some who suffer with OSA have tested with higher bone mineral density. For example, a study that applied an OSA model of intermittent hypoxia on 7 week old rats, showed improved BMD through osteogenesis and increases in HIF-1 and VEGF (Oishi et al., 2016). Additionally, Sforza et al. (2013) found that the BMD of elderly men with OSA was preserved, potentially due to the same factors that preserved and increased bone in less severe, more moderate doses of implemented therapeutic hypoxia. Clearly, more research is warranted in this area as it has an opportunity to compete with pharmacological treatments for osteoporosis. Many studies have found that more moderate OSA vs severe OSA has the potential to produce not only improved bone, but also unexpected longevity in the elderly (Lavie & Lavie, 2009). Therefore, it could be that when OSA is of a milder status that the body is able to adapt to over time, the positive adaptive traits that result in improvements in areas such as bone and longevity are in direct contrast to the inflammation and chronic disease that stems from severe OSA, in which the body never has the opportunity to recover, leading to exhaustion and maladaptation (Selye, 1950).

11.3 Bone & Breath

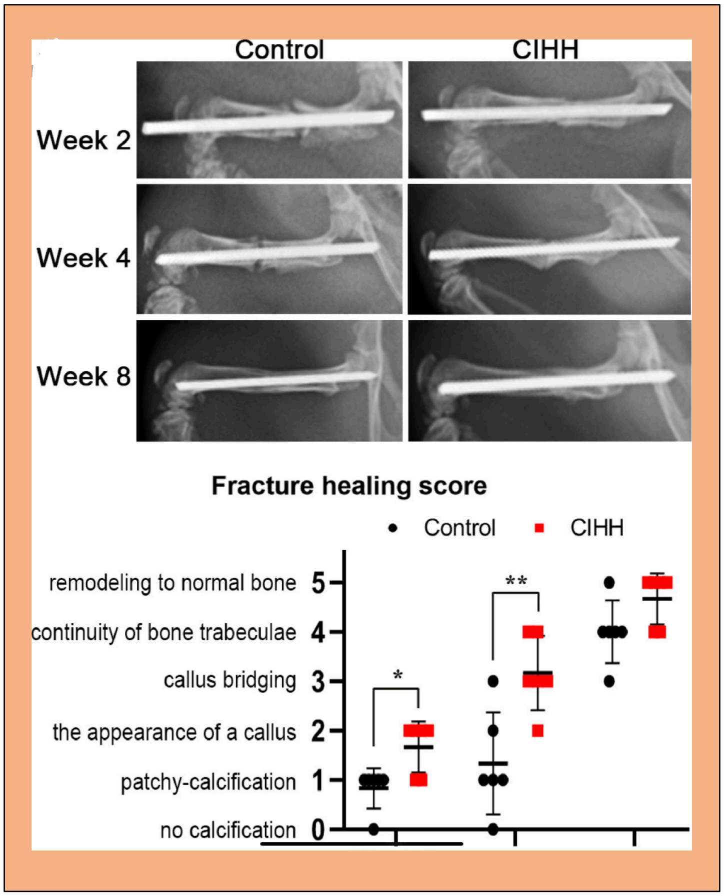
Not only can adding an emphasis on breath specificity while working out benefit muscle strength and mobility, cognition, and lung/respiration longevity markers, but it also has the potential to profoundly affect the skeletal system through better functioning biomechanics that lead to less injury, and stronger, more metabolically active muscle tissue that can lead to higher bone density (Kaji, 2014; Suominen, 2006). As mentioned earlier, slow breathing at six breaths per minute increases HRV, which is strongly associated with a better balance of sympathetic and parasympathetic nerve activity regulating blood flow and activity in the muscle (Ernst, 2017). Higher HRV measurements are associated with healthier muscle tissue that ultimately has the ability to become stronger and put more tension on the bone that it connects to, which more effectively applies Wolf's Law that states repetitive that loading of the bone will cause positive adaptations in the bone (Debeck et al., 2010; Teichtahl et al., 2015). Miyasaka et al (2013) found a strong relationship between low HRV score and decreased bone density in perimeopausal women. The authors conclude that more research is needed in the area of improving HRV scores in this group. Furthermore, Kuryami et al. (2017) found a high association between sympathetic nervous system hyperactivity and bone loss. Slow breathing has been shown to be a highly effective strategy in increasing HRV through the reduction of the sympathetic nervous system's activity, while bolstering the bone-promoting parasympathetic nervous system (Russo et al., 2017). Not only has breathing at 6 breaths per minute been shown to increase HRV scores, but also, as mentioned in the above sections, is both cardio and neural-protective through creation of EPO and NO, increasing the efficacy of an IHT or IHE protocol (Camacho-Cardenosa et al., 2019). Because EPO and NO are factors that also contribute to healthy bone remodeling, the combination of breath work and intermittent hypoxia envisages bright horizons.

In addition to slowing the breath down in order to reduce the risk of declining bone mineral density through improved HRV scores, integrating forceful exhalations intermittently throughout a work-out could aid in exercise program consistency through the prevention of program-ceasing injuries. There is a higher percentage of activation of the low back stabilizing core musculature such as internal oblique, external oblique, and transversus abdominis when forcefully exhaling, which, when strong and active, have been shown to prevent injury and pain not only in the low back, but the entire kinetic chain (Bliven & Anderson, 2013; Ishida et al., 2017). Long-term adherence to a well-programmed and periodized exercise macrocycle has been shown to result in the most significant improvements in body composition with increases in lean muscle mass, reductions in fat loss, and increases in bone density (Evans, 2019; Lorenz & Morrison, 2015). An increase in muscle mass provides the tension on the bone that is necessary to achieve the aforemetioned Wolf's Law (Teichtahl et al., 2015). Furthermore, the significant increases in core musculature such as the transversus abdominis when performing forceful exhalations, have the potential to not only prevent injury, but also improve lumbar spine bone mineral density because of the muscle's insertion into the thoracolumbar fascia that connects to and creates tension on the lumbar vertebrae (Avin et al., 2015).

Slow exhalations, forceful exhalations, and voluntary apneas not only are injury preventative, but also have the potential to intermittently bring the blood oxygen saturation levels down to approximately 85% throughout the work out, which has the has ability to stimulate VEGF producing HIF-1 that contributes to bone angiogenesis (Woorons et al., 2014). Proposed future research to benefit those suffering from or at risk for osteoporosis is necessary. More human IHT research using exercise protocols with reduced FiO2 levels for the post-menopausal women group, who are most at highest risk for osteoporosis due to lower estrogen levels, is direly needed (Cauley, 2015). Theoretically, follow-up research on the same cohort of post-menopausal women could include experiments that look at the effects of breath-induced intermittent hypoxic training (*BIIHT*) in order to clarify if performing a specific breathing routine in conjunction with exercise has the potential to improve bone mineral density more than just exercise alone. Much more work needs to be done in this area, but it is an area that needs attention as the fracture rates associated with post-menopausal women diagnosed with osteoporosis are 1 in 3 women (Geyer, 2016).

Because of the aforementioned benefits of combining voluntary breathing and intermittent hypoxia, it is recommended that as an osteoporosis preventative and therapeutic strategy, application of these non-pharmacological treatments, delivered through a bone-stimulating total body exercise routine, is implemented. A *BIIHT* program has the potential to effectively deliver a combination of HRV-lowering voluntary breathing, bone-stimulating intermittent hypoxia, and bone-loading exercise for those suffering from bone loss or who would like to employ a preventative strategy. Much more research is needed in this area to observe the effects of a convenient, at home routine on BMD. As of now, a proven strategy of exposing oneself to lower levels of FiO2 while exercising in an IHT protocol, during which slowing down the breath can serve as a physiologically protective and bone-enhancing component, is recommended as a low risk tool that benefits most who implement it with little to no known risk or side-effects.

Figure 28



Note: Bone healing markers over 8 weeks post fracture in two groups: control and CIHH (chronic intermittent hypoxia). Adapted from "Chronic Intermittent Hypobaric Hypoxia Enhances Bone Fracture Healing.", by Zhang, L., Jin, L., Guo, J., Bao, K., Hu, J., Zhang, Y., Hou, Z., & Zhang, L. (2020). *Frontiers in Endocrinology (Lausanne)*, 11, 582670–582670. https://doi.org/10.3389/fendo.2020.582670

CHAPTER 12

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Although there has been decades of research in the area of utilizing intermittent hypoxia as a therapeutic and performance enhancing strategy, it is still in its infancy stages in terms of full exploration of the vast potentials and the proper dosing. New scientific technologies continue to arise that, with application to IHE and IHT, unveil deeper insights into the mechanisms behind the adaptive processes of the human body to altitude and intermittent hypoxia. For example, proteomics is the study of the organism's system wide proteins and their interactions (Chandramouli & Qian, 2009). Proteomics, first implemented in 1975 by O'Farrell, Klose, and Scheele, has advanced from the studying of single proteins to a study of the relationship between the vast array of proteins in the entire body (Patterson & Aebersold, 2003). Recently, proteomics has been used to study AMS, acute mountain sickness, through the body's adaptive response to hypoxia (Julian et al., 2013). This has lead to a deeper understanding of the mechanisms behind an adaptive vs maladaptive dosing of hypoxia, in addition to methodologies for preventing poor responses to altitude and hypoxia by creating a more successful "pre-conditioning" strategy (Lu et al., 2018).

The mapping of the human genome was a scientific breakthrough that has left no branch of science untouched (Schuler et al., 1996). Moving into the world of genetic testing, which enables an individual to become educated on their genetic profile for the purposes of preventative medicine, the horizons are vast in terms of utilization of intermittent hypoxic and breathing protocols as preventative strategies (Serebrovska et al., 2016). If a genetic profile indicates that a person is at risk for development of asthma or emphysema, breathing exercises in combination with exercise and intermittent hypoxia should be utilized as a preventative tool that is low-risk with no side effects (Vogtel et al., 2010).

No human body benefits from the absence of exercise. Dosed appropriately, exercise has the ability to extend life-span and keep chronic disease at bay (Booth et al., 2010). Therefore, implementation of solely a structured exercise routine can reduce the risk of advanced all-cause mortality by a significant degree (Lee & Skerrett, 2001). That being said, exercise alone has not been shown to improve the age-related decline in respiration strength and lung function to the magnitude that respiration exercises have (Shei, 2018). Therefore, it would seem a life-span robbing crime to not include a respiratory strengthening, voluntary breathing routine into the mortality reducing exercise program already implemented. Considering that the aforementioned breathing routine *BIIHT* also strengthens the injury-preventing core in conjunction with the respiratory muscles, it may be a suggested protocol that IHT methods must combine a voluntary breathing routine such as this for maximum benefit with least possible risk.

Consistency is key for long-term results. A workout that is not only disease and injury preventative, but also time and cost-efficient is necessary. While traditional IHT and IHE protocols using altitude, hypoxic chambers, and hypoxicators have shown high efficacy with little to no risk, the time and cost component would cause most of the healthy population to not consider this is a viable option for health and longevity. Therefore, more research in the area of creating an effective IHT routine that is convenient and low-cost is necessary. If implementation of a *BIIHT* routine could enable a healthy exerciser to garner even a fraction of the benefits that have been documented in the decades of IHT, IHE and paced-breathing research, there could be a future of declining numbers of the risk factors that lead to increased rates of all-cause mortality in conjunction with a global population that is not mentally and physically stressed with obesity and low heart rate variability. Instead, obesity will no longer be the most common trait in the world, but strength will. Existing in a state of sympathetic fight or flight will no longer predominate, but strong parasympathetic nervous systems will reign strong with the coinciding calm thoughts and interactions that are conducive to equanimity, not anxiety and depression. There is bright potential on the horizon of intermittent hypoxia combined with voluntary breathing with implementation into an exercise routine that both strengthens and calms the mind and the body. Advancements in science, continuation of research, and spreading the word of the importance of finding effective methodologies to prevent and treat chronic disease are vital factors in creating a stronger movement in the area of intermittent hypoxia and voluntary breathing routines.

"You must be the change you wish to see in the world."

- Ghandi

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APPENDIX A

Hypothetical Study # 1	Body Composition Improvement superior in IHT and BIIHT in comparison to Normoxia and Normal Breathing
Hypothesis	If BIIHT is performed while performing a total body routine, fat loss will be greater than those training without BIIIHT, but not more than those training in hypoxia (IHT will be greater or equal to BIIHT)
Methods	ALL groups are given dexa scan test at the beginning and at the end of a 12 week trial in addition to measuring lean mass, blood lipids, substrate use during and after exercise, blood glucose, and blood insulin levels.
CONTROL Group A	Total body exercise routine in normoxia with NB
Experimental Group B	Total body exercise routine in normoxia with BIIHT
Experimental Group C	Total body exercise routine in hypoxia 15% FiO2

APPENDIX B

Hypothetical Study # 2	Cognitive Enhancement in Motor Learning comparing IHT, NT, and CT
Hypothesis	If BIIHT is performed while learning a new skill, motor learning will improve in comparison to those training without breathing, but not more than those training in hypoxia.
Methods	ALL groups are given a memory test before and after each session and have MRI imaging of brain at the beginning of the 12 week trial, during workout sessions, and at the end of the 12 week trial, looking for increased neurogenesis in the hippocampus. Workouts are 3x per week for 45 minutes using 15% FiO2 for IHT, 21% FiO2 for normoxia control group with breathing normally (BN) and 21% FiO2 group for normoxia group with BIIHT.
CONTROL Group A	Total body exercise routine in normoxia with NB
Experimental Group B	Total body exercise routine in normoxia with BIIHT
Experimental Group C	Total body exercise routine in hypoxia 15% FiO1

APPENDIX C

RECOMMENDED DOSING	BIIHT
60 minute sessions 3x/week	Combination of cardiovascular and total body strength coinciding with specific voluntary breath work
Between 3-6 breaths/minute	Shown to activate PNS, parasympathetic nervous system
Breathing Normally (BN)	Inhale for 2 seconds, exhale for 8 seconds (on effortful concentric contraction)
Short Breath (SB)	loud and aggressive forceful exhalation, pulling navel to spine, on "Shhhh" sound
Long Breath (LB)	less aggressive rate of exhale. Blow through pursed lips 3 seconds, hiss for 3 seconds, soft "shhhh" for 3 seconds, loud "shhh" for 3 seconds. Inhale for 1 second only aggressively (full tidal volume)
Voluntary Apnea (VA)	breath hold varying from 4-10 seconds
Activation Double SHUT (DS)	brace in ribs then navel 2 beats (see McGill bracing technique)

Long Inhales (LI)	vary between 3-6 inhales with breath holds in between (Herring Breur Reflex for parasympathetic nervous system)
Belly Pulse	Pumping the navel in with transversus abominis either quick contractions or slow held pulse for sustained ADIM (abdominal draw-in maneuver)

Note: Breakdown of breath components of hypothetical *BIIHT* protocol. This table can be used to be applied to future research comparing traditional IHT protocols with *BIIHT* protocols.

APPENDIX D

SAMPLE *BIIHT* WORKOUT

Teaser Ab – Hands Push for EO
3 X 12:

1. LB
2. SB with 4 second VA
3. LB with 2 second VA

Teaser Ab – Keep Eye on Oximeter
3 X 12:

1. LB
2. SB with 4 second VA
3. LB with 2 second VA

Isometric Anti-Rotation
3 X 12:
1. LB
2. SB with 4 second VA
3. LB with 2 second VA

Dynamic Mid-Height Chop
3 X 12:
1. LB
2. SB with 4 second VA
3. LB with 2 second VA

Plank – Watch Oximeter for SpO2 Drop
3 X 12:

1. LB
2. SB with 4 second VA
3. LB with 2 second VA

Bird Dog – Watch Oximeter
3 X 12:

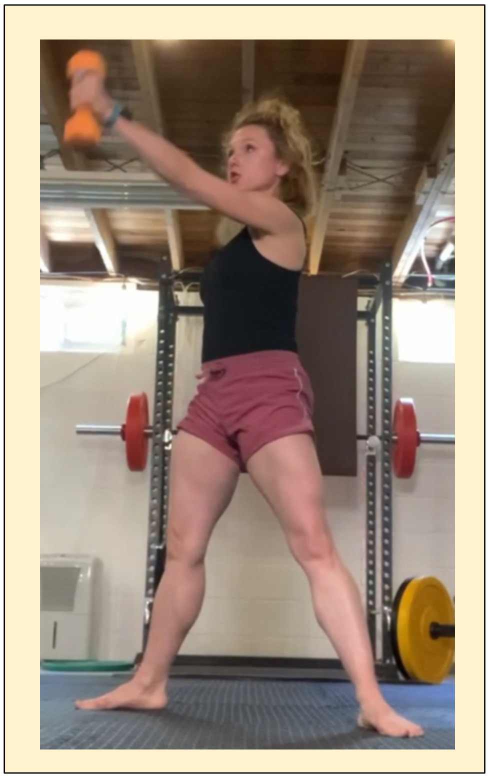
1. LB
2. SB with 4 second VA
3. LB with 2 second VA

Single KB Swing
3 X 12:

1. LB
2. SB
3. LB with VA 2 seconds

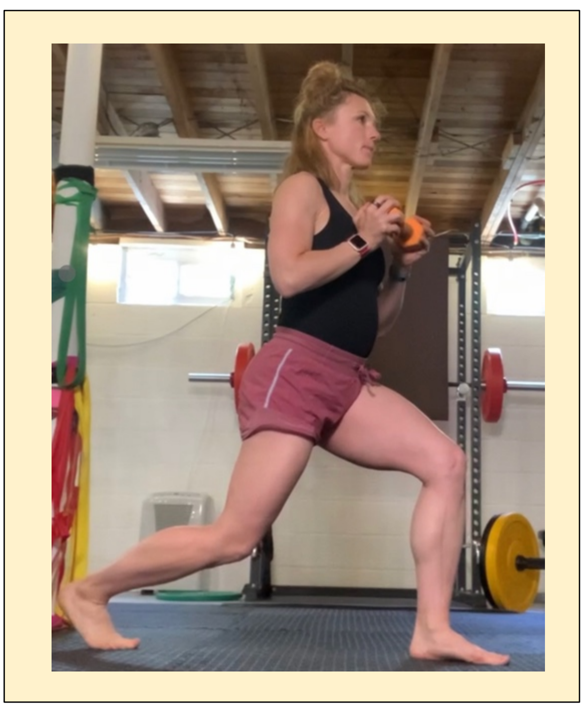
Sumo Drop
3 X 12:

1. LB
2. SB
3. LB with VA 2 seconds



Deep Squat with KB Swing
3 X 12:

1. LB
2. SB
3. LB with VA 2 seconds



Static Lunge Watch SpO2
3 X 12:

1. LB
2. SB with 4 second VA
3. LB with 2 second VA

Mobility Hip flexor
1 X 15:
1. LB with 4 second VA

Squat ISO and Row
3 X 12:
1. LB
2. SB with 4 second VA
3. LB with 2 second VA

ADDITIONAL NOTES

BIIHT

From an anecdotal perspective, there is the classic “Type A” individual or the the hard-driving competitive athlete, who needs a workout-out that is mentally and physically challenging in order to feel accomplished, increasing intra-workout satisfaction, which is a contributing factor to consistency (Liem, 2018). Personal trainers, while not intentional, may have the ability to do more harm than good as they apply the challenging methods that their client is requesting in order to retain that client as a customer. Sports periodization science shows not only athletes, but also the general population benefits from the method of periodization, which strategically fluctuates in an inverse manner the volume and intensity of the program over the course of the year in order to prevent injuries and overtraining fatigue, stemming from peripheral and central mechanisms (Lorenz & Morrison, 2015). “Over-achieving” clients and athletes may not be open to reducing the intensity of their workout unless they are recovering from or have an injury. Integrating breath-induced intermittent hypoxia intra-workout has the potential to induce a higher metabolic workload while doing less impactful activity (Woorons et al, 2010). This higher perceived exertion while performing lower impact work could assist in the sensation that the body is working maximally without the intensity level being chronically high, which would lead to over-training syndrome (OTS) or injury (Kreher & Schwartz, 2012).

Exercise is a known effective method of improving the cardiovascular, circulatory, skeletal, nervous, lymphatic and digestive systems (Vina et al., 2012). This paper did not delve into the effects of exercise training on the bodily systems as this was not the focal point of the thesis, but it warrants mentioning that adding coupling the proposed *BIIHT* with cardiovascular and strength training has the ability to allow the patient/client to reap the benefits of breath, intermittent hypoxia and exercise. It has been shown that combining voluntary breathing with exercise is an effective method to not only increase activation levels of injury-preventative core muscles while vigorously moving the body, but also improves motor learning through down-regulation of the anxiety provoking sympathetic nervous system (Ishida et al., 2016; Yadav et al., 2016). In addition, active IHT has been shown to be as, if not more, effective than passive IHE in athletic improvements, hypertension improvements, fat loss, muscle gain, and cognitive decline improvements (Guardado et al., 2020; Serebrovska et al., 2016). The proposed method of *BIIHT* is ideally performed with aerobic or anaerobic cardio and strength training in order to achieve the maximum benefits of improving health and becoming stronger both peripherally and centrally.