A Thesis

entitled

The Effects of High Intensity Interval Training (HIIT) on Asthmatic Adult Males

by

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This study examined pulmonary function, ventilation, exercise tolerance and the fractional concentration of exhaled nitric oxide (FeNO) in healthy controls (CON; n=7) and asthmatics (ASTH; n=7) following two-weeks of high intensity interval training (HIIT). An increase in FeNO above basal levels is associated with lung inflammation and is gaining popularity as a reliable diagnostic tool for the treatment of asthma.

**PURPOSE:** The extent that HIIT decreases FeNO and thus, exercise tolerance in asthmatic subjects has not been previously investigated. **METHODS:** Pulmonary function was assessed using peak expiratory flow [PEF], forced vital capacity [FVC], and the ratio of forced expiratory volume in one second to FVC [FEV1/FVC]. FeNO was measured noninvasively using a NIOX portable device. Both groups performed a progressive exercise test (20 W/min) on a cycle ergometer to determine peak values of O2 uptake (VO2peak), CO2 output (VCO2peak), ventilation (VE) and time to exhaustion (TTE). Each subject completed six sessions of HIIT, which included 8 minutes of loadless cycling warm-up, 10 x 60 s bouts of exercise interspersed with 60 s periods of recovery at a low intensity of cycling. The intensity of the HIIT protocol was set at a target equivalent to 75% peak WR for ASTH and 80% peak WR for CON. Each training
session was followed by 5 minutes of loadless cycling cool down. Following completion of all HIIT sessions, each subject repeated the pulmonary and exercise tests that were performed prior to training. A two-way analysis of variance with repeated measures (ANOVA-RM) was used to examine main effects, group (CON vs. ASTH) and time (Pre-vs. Post-HIIT) and significant interactions (Group x Time). A Student Newman Kuels post hoc test was used to determine specific differences as appropriate. Statistical significance was set at p < 0.05

RESULTS: Significant differences were found between the groups in FeNO, VO\textsubscript{2peak}, TTE, and peak WR. No differences were found between or within the groups in the pulmonary function measures. The pre-HIIT mean ± SEM of FeNO was 28 ± 2 ppb in ASTH versus 18 ± 1 ppb in CON and post-HIIT 28 ± 2 ppb versus 16 ± 3 ppb. The pre-HIIT mean ± SEM of TTE in ASTH was 691 ± 40 s and in CON was 998 ± 23 s, while post-HIIT TTEs were 781 ± 41 s and 1033 ± 36 s respectively. Pre-HIIT peak WR in ASTH was 175 ± 13 W and in CON 290 ± 10 W, while post-HIIT was 203 ± 14 W in ASTH versus 302 ± 13 W in CON.

CONCLUSIONS: The HIIT was well tolerated by the ASTH subjects, and they were able to achieve a higher VE, VCO\textsubscript{2}, TTE, and peak WR following 6 sessions on HIIT.
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List of Abbreviations

ASTH.................................Asthmatic group
ATS.................................American Thoracic Society
CON.................................Control group (non-asthmatic)
DCs.................................Dendritic cells
EIB.................................Exercise induced bronchoconstriction
ERS.................................European Respiratory Society
FeNO.................................Fractional concentration of exhaled nitric oxide
FEV₁.................................Forced expiratory volume in one second
FVC.................................Forced vital capacity
FEV₁/FVC............................The ratio of forced expiratory volume in one second to forced vital capacity
HR.................................Heart rate
NO.................................Nitric oxide
PEF.................................Peak expiratory flow
PWR.................................Peak work rate
TTE.................................Time to exhaustion
VE.................................Minute ventilation
VCO₂.................................Carbon dioxide output
VO₂.................................Oxygen uptake
WHO.................................World Health Organization
Chapter 1

Introduction

Asthma is a common chronic inflammatory disorder of the airways in which cells and cellular elements such as mast cells, eosinophils, T-lymphocytes, B-lymphocytes, macrophages, neutrophils, and epithelial cells play various roles. In asthmatic individuals, this inflammation can cause recurrent symptoms such as wheezing, chest tightness, shortness of breath, and coughing (Lieberman 1999; National Institutes of Health [NIH] 2007). It is a global health problem affecting nearly 300 million individuals worldwide, of all ages, ethnic groups and regions (Bousquet et al. 2009). Asthma contributes to nearly 250,000 premature deaths each year around the world (Bousquet et al. 2009). In addition, asthma is more prevalent in urban populations than rural ones, which may be the result of differing levels of physical activity and environmental allergens, though the reasons for the difference are not completely known (Lucas et al. 2005).

Regular physical activity in both healthy and at-risk populations has preventative effects on the development and worsening of asthma (Lucas et al. 2005; Rosenkranz et al. 2012). Key factors affecting the impact of physical activity include type and severity (Mendes et al. 2011) of asthma as well as the intensity and duration of the activity (Emtner et al. 1996). Unfortunately, lifestyle issues such as limited time and anxiety about exercise can create obstacles to maintaining a regimen of regular physical activity.
As a result, there is a need for a time-efficient and beneficial exercise program that can prevent and attenuate the symptoms of asthma, whether alone or in combination with pharmaceutical treatments. One approach to exercise called high-intensity interval training (HIIT) in particular shows a lot of promise.

1.1 Pathophysiology

In general, the causes of asthma are multifactorial, including contributions from allergen exposure, hygiene, and lifestyle (Lucas et al. 2005). The hallmarks of asthma are bronchoconstriction, airway edema, airway hyperresponsiveness, and airway remodeling (NIH 2007). While the root causes of asthma are widely debated, a typical extrinsic asthma episode begins with a trigger (such as an allergen) that alpha-1 receptors in the bronchial wall detect as an invasive particle. As a result, the smooth muscle of the airway constricts, histamine and other mediators are released causing edema and increased secretion of mucus into the airway lumen to trap more of the allergens; collectively, these reactions restrict flow through small airways (Leiberman 1999). In the case of intrinsic asthma, for instance during exercise, the major cause of exercise-induce bronchoconstriction (EIB) is hyperpnea, which leads to the rapid air flow through the bronchi. The two factors appearing to play a role are the cooling of the airway and the evaporation of the water from the airway surface that occur due to hyperpnea. More blood rushes to the bronchial tubes for heating which ultimately leads to swelling and reduction in the size of the airway lumen (Leiberman 1999). Unfortunately, because the triggers of asthma are multifactorial, the effect of exercise can be complicated. While exercise has long-term preventative benefits on asthma in general, at the same time it carries a short-term risk as a potential trigger for EIB sufferers.
1.2 Nitric Oxide

One of the consequences of the cascade of inflammatory reactions during an asthma attack is the release of nitric oxide (NO). Nitric oxide (NO) is a potent vasodilator created in large part by the action of inducible NO synthase (NOS) in the epithelial cells of the airway (National Institute of Health, 2007). According to the American Thoracic Society (ATS), exhaled NO may reflect distal lung inflammation and is increased in patients with severe asthma (Dweik et al. 2011). Measurements of fractional exhaled NO (FeNO) may be useful in diagnosing and monitoring treatment response because of the correlation between FeNO and the level of inflammation (WHO 2007). As a diagnostic tool, FeNO can help measure the effect of exercise on lung inflammation in asthmatics. Bonsignore et al. (2008) and Morreira et al. (2008) have used it as a measure of inflammation for the effectiveness of exercise on asthmatic children, while Mendes et al. (2010) measured FeNO adults. However, despite its usefulness as an indicator of inflammation among asthmatics, no other studies have used it to measure the effectiveness of exercise as a treatment.

1.3 Benefits of Physical Activity

It has been widely demonstrated that regular exercise protects against all-cause mortality, including heart disease, Type II diabetes mellitus, obesity, chronic obstructive pulmonary disease (COPD), and atherosclerosis (Petersen & Pedersen, 2005). Even though many factors contribute to the development of asthma, the role of physical activity seems to attenuate the effects of asthma although its role is not well understood (Rosenkranz et al. 2012). Physical activity has been shown to also have cardiovascular benefits for asthmatics, although pulmonary benefits are weak (Mendes et al. 2011; Ram
et al. 2000). Conversely, lack of physical activity, particularly from moderate to high intensity, is believed to increase the risk of asthma (Rosenkranz et al. 2012). Both Bonsignore et al. (2008) and Rosenkranz et al. (2011) hypothesized that physical activity decreases hyperresponsiveness in at-risk asthmatics by stretching and relaxing the airway and airway smooth muscle.

The effects of physical activity on chronic diseases have focused on aerobic training, which can be further distinguished by intensity and duration. On the extremes are endurance training (ET) and HIIT, in which the former is low intensity over a long duration while the latter is high intensity over a short duration (Dunham & Harms 2012). Specifically, HIIT is characterized by brief, intermittent bursts of vigorous activity interspersed with periods of rest or low-intensity exercise (Gibala et al. 2012). Traditionally, ET has been the preferred method for performance improvement, rehabilitation, and disease treatment (Dunham & Harms 2012). However, the benefits of HIIT are being increasingly studied.

1.4 Safety of HIIT

HIIT has been shown to improve pulmonary function in healthy subjects just as well as ET, but in a more time-efficient manner (Dunham & Hams 2012). However, HIIT may not be appropriate in all cases because it may pose a health risk to push some subjects with chronic diseases to high-intensity levels of exercise. Despite this possible risk, most studies have shown HIIT is safe for a variety of chronic diseases. Normandin et al. (2013) showed HIIT is well-tolerated and even beneficial for congestive heart failure patients who are young males with few comorbidities. Likewise, for patients with type 2 diabetes, HIIT was shown to be a safe as well as effective treatment (Gillen et al.
HIIT has also been shown to be safe and effective for overweight young males while also decreasing fat and increasing muscle mass (Heydari, Freund & Boutcher 2012). Because of findings such as these and others, Shiraev and Barclay (2012) concluded that HIIT is both safe and effective for patients with diabetes, stable angina, heart failure and post-myocardial infarct.

As for asthma, the evidence regarding the safety of HIIT is not as well-investigated, but in the few studies that have applied HIIT to asthmatic subjects, the protocol appears to be safe. Emtner et al. (1996) submitted twenty-six asthmatic subjects to HIIT aquatic exercises; none of the subjects were injured and all were able to maintain the very high intensity exercise without asthma symptoms. Not only was HIIT safe for these asthmatic subjects, but the investigators showed the intervention improved both cardiovascular fitness and, unlike non-HIIT studies, pulmonary function (Emtner et al. 1996). Moreover, the ATS and ERS stated it is safe and even recommended that individuals with asthma exercise at 60 to 75 % of VO_{2max} 2 to 5 days per week for 20 to 30 minutes (Nici et al. 2006).

1.5 Statement of Problem

People with asthma tend to avoid exercise out of fear of triggering an attack (Chandratilleke, Carson, Picot, Brinn, Esterman & Smith 2012), despite the demonstrated benefits of some types of exercise on cardiovascular health, exercise tolerance, and pulmonary function even for asthmatics (Mendes et al. 2011). Additionally, a common reason for not participating in regular physical activity is a lack of time. Given the widely supported health benefits of HIIT in individuals with diabetes and heart disease (Petersen & Pedersen 2005) and the positive impact of low- (Cochrane & Clark 1990) and
moderate-intensity training (Boyd et al. 2012) on adults with asthma, an HIIT routine for asthmatic adults can potentially be a time-efficient and effective way to improve health.

However, very few studies have been conducted on the effect of HIIT on asthmatic adults. The one study of HIIT and asthmatic adults that has been conducted focuses on swimming as the HIIT protocol and was conducted seventeen years ago (Emtner, Herala & Stalenheim 1996), so there is a gap in the literature focusing on non-aquatic HIIT on asthmatic adults. Most studies that investigate the effect of exercise on asthma either use children as their subjects or apply low- to moderate-intensity training protocol. Moreover, although strong support exists for the diagnostic value of FeNO in determining lung inflammation in asthmatics (Grzelewski et al. 2012), only one study has investigated the effect of physical activity on FeNO levels in asthmatic adults (Mendes et al. 2011). Therefore, there is a need to determine the effect of HIIT on asthmatic adults as a time-efficient and beneficial way to encourage asthmatics in regular physical activity.

1.6 Statement of Purpose

The purpose of this thesis is to determine if HIIT reduces lung inflammation and improves pulmonary function among adults with asthma. For the purposes of this study, lung inflammation was determined by measuring FeNO and pulmonary function was determined by forced expiratory volume in one second (FEV₁), the FEV₁ to forced vital capacity ratio (FEV₁/FVC) and peak expiratory flow (PEF).

1.7 Research Questions

Given this background, the research question for the proposed study was; does high intensity interval training (HIIT) reduce lung inflammation and improve pulmonary function and cardiovascular fitness among adults with asthma?
Chapter 2

Literature Review

Regular exercise protects against all-cause mortality, including heart disease, diabetes mellitus Type II, obesity, chronic obstructive pulmonary disease (COPD), and atherosclerosis (Petersen & Pedersen 2005). For asthma, exercise has been known to have some therapeutic benefits at least as early as Salter (1882), who concluded prolonged bodily exertion can be of great benefit to an asthmatic individual, although he further noted that the treatment is prophylactic rather than curative. Indeed, decreased physical activity over the past 50 years has likely led to the observed increase in the occurrence of asthma during the same course of time (Lucas et al. 2005). At the same time as it is beneficial for some asthmatic individuals, exercise may pose some risk for those with EIB (Anderson & Kippelen 2005). However, even in individuals with EIB, exercise can be safe with administration of short-acting β₂-agonist (SABA) before exercise because of the high responsiveness of EIB to treatment (Lucas et al. 2005; Dweik et al. 2011).

2.1 Categorization of Asthma

The effectiveness of exercise on asthma may vary depending on severity of the condition (Mendes et al. 2010), so it is useful to understand how severity can be defined.
Concepts such as severity and control are important for evaluating and treating asthmatic patients, but unfortunately the terminology is not standardized (Bousquet et al. 2009). Typically, the severity of asthma is categorized as mild intermittent, mild persistent, moderate persistent, or severe persistent (National Asthma Education and Prevention Program [NAEPP], 2010). Mendes et al. (2010) found a more significant reduction of signs of inflammation among subjects with more severe asthma following an exercise program.

In addition to severity, some authors classify various manifestations of asthma as different “phenotypes.” A variety of classification schemes are employed to define differences among phenotypes. For example, asthma may be categorized by its cause/trigger, which can be either extrinsic or intrinsic. Extrinsic asthma, or sometimes called exogenous asthma, describes allergies that are triggered by external factors, namely allergens such as pollen, dust, and pollution (Chen et al. 2012). In contrast, intrinsic asthma, also referred to as endogenous or non-allergic asthma, is triggered by internal causes, including stress, infection, exercise, and medication (Chen et al. 2012). Extrinsic asthma is more common in children while intrinsic asthma is more common in adults (Chen et al. 2012). Approximately 90% of children have a strong allergic component and 50-60% of adults have asthma that can be provoked by allergies to some extent (Lieberman 1999).

Asthma can also be categorized according to the role played by various cellular components such as T-helper lymphocytes. For example, Wenzel (2012) has proposed a scheme where certain phenotypes (including the most common—extrinsic allergic) are characterized by high levels of inflammation, while others such as aspirin induced may
demonstrate only very low levels of inflammation. At this point a clear, unambiguous, functional classification scheme for different manifestations of asthma remains elusive.

2.2 Pathophysiology

The hallmarks of asthma are bronchoconstriction, airway edema, airway hyper-responsiveness, and airway remodeling (NIH 2007). In general, the causes of asthma are multifactorial, including contributions from allergen exposure, hygiene, and lifestyle (Lucas et al. 2005). The wide range factors contributing to asthma has led to further classification of the condition into two major types based on the differing triggers and patterns: extrinsic and intrinsic asthma (Lieberman, 1999). Extrinsic asthma is characterized by external triggers such as allergens and pollution, while intrinsic asthma is characterized by internal triggers such as the hyper-responsiveness of the airway to dryness and cooling during exercise.

While the root causes of asthma are widely debated, a typical extrinsic asthma episode begins with a trigger (such as an allergen) that alpha-1 receptors in the bronchial wall detect as an invasive particle. As a result, the smooth muscle of the airway constricts, histamine and other mediators are released causing edema, increasing secretion of mucus in the lumen to trap more of the allergens; collectively, these reactions limit airflow (Leiberman 1999). In the case of intrinsic asthma, however, the major cause of exercise-induce asthma is hyperapnea, which is the production of rapid airflow through the bronchi. The two factors that appear to play a role in intrinsic asthma are the cooling of the airway and the evaporation of the water from the airway surface that occur due to hyperventilation. More blood rushes to the bronchial tubes to heat the area, which ultimately leads to swelling and reduction in the size of the airway lumen (Leiberman...
1999). One of the side effects of this inflammatory reaction is the release of nitric oxide (NO).

### 2.2.1 Extrinsic Asthma and Allergies

Extrinsic asthma is essentially a condition caused by immune system imbalance and oversensitivity. The immune system comprises two subsystems usually called the innate immune system and the adaptive (or acquired) immune system (Holgate 2012). The innate system is the first line of defense against any invading agent (including parasites, infective bacteria, viruses, etc.) (Holgate 2012). It is also the immune system humans are born with, hence the name innate. It is characterized by a broad but shallow defensive approach to foreign agents. The primary cells of the innate immune system that contribute to extrinsic asthma include leukocytes, mast cells, eosinophils, macrophages, and neutrophils (Holgate 2012).

In contrast to the innate immune system, the adaptive system is the second line of defense to any potential threat, and is triggered whatever foreign agents and particles the innate system detects and communicates to this second wave of attack (Holgate 2012). Humans are not born with most of the cells and cellular components that the adaptive system comprises; rather, human bodies adapt, or acquire, this system over time based on the environment and exposure to various threats, hence its name (Holgate 2012). It is characterized by a targeted and intense defensive approach against invasions. The primary cells involved in the adaptive system are T-lymphocytes. The most influential types of T-lymphocytes in asthma are T-helper 2 (TH2) cells and B-lymphocytes, along with their various subcellular components, such as the allergic antibody Immunoglobulin E (IgE) (Holgate 2012).
In people with extrinsic asthma, the immune is oversensitive to foreign particles and agents that are not necessarily harmful (Holgate 2012). In particular, it is likely the adaptive immune system that is over-reactive to particles such as dust, pollens, animal dander, and pollutants (Holgate 2012). Extrinsic asthma is more common among children (Lieberman 1999), which adds support to the theory that it is the adaptive system that is poorly calibrated in this type of asthma. Since children are not born with an adaptive system and are in the process of developing it, it is likely that the adaptive system is more prone to imbalances in its development.

Although the way these two parts of the immune system interact to create asthma in is not completely known, recent research has helped develop a rough outline of multiple possibilities. The dominant theory is that the starting point of developing extrinsic asthma is the activity of dendritic cells (DCs) (Holgate 2012). DCs are antigen-presenting cells that occur in high numbers in places on the body that are exposed to the external environment, such as the skin, throat, and lungs (Holgate 2012). Within the lungs, DCs are found on the surface of the airway tubes. These DCs detect various potential threats and deliver them to the T-lymphocytes, so for this reason they are considered the first point of communication between the innate and adaptive immune systems (Banchereau & Steinman 1998). The T-lymphocytes react to signals from DCs by either sending messages to helpful or harmful cells, depending on whether the antigen is perceived as harmless or threatening. If detected as a threat, then T-lymphocytes, as conductors of the adaptive immune system, begin to mobilize other cells to fight against this perceived threat (Lieberman 1999).
One communication path is from T-lymphocytes to B-lymphocytes, which tells B-lymphocytes to manufacture antibodies such as IgE (Holgate 2012). IgE is a key component of allergic reactions, because it activates many of the innate immune cells such as mast cells, eosinophils, neutrophils, and macrophages (Holgate 2012). The other path involves messages sent from T-lymphocytes to the specific T-cells, called TH2 cells. Asthmatic individuals have an imbalanced T-cell profile that favors TH2 cells (Lieberman 1999). These TH2 cells manufacture cytokines such as interleukin-4 (IL-4), IL-5, IL-10, and IL-13 (Lieberman 1999). The role of these interleukins is to activate other leukocytes whose function is to either trap or kill what is perceived as a potential parasite (Lieberman 1999).

The outcome of this series of reactions to a perceived threat is inflamed tissue, increased mucous production, smooth muscle constriction, and increased leukocyte activity designed to catch and eliminate a threat that in the case of asthmatics is not really a threat. As a result, asthmatics during an attack experience shortness of breath, wheezing, and coughing, all in reaction of a misperceived threat.

2.2.2 Intrinsic Asthma and Exercise Induced Bronchoconstriction

Although exercise can potentially improve asthmatic individuals’ tolerance of allergens and reducing the frequency and severity of attacks over time as long as they manage it with controller medications, one widely known shortcoming of exercise as the fact that it can induce asthma in some individuals (Anderson & Holzer 2002). Exercise induced asthma, more generally known as exercise induced bronchoconstriction (EIB), occurs when the strain of exercise on the airways triggers asthmatic reactions (Anderson & Holzer 2002). In the first few minutes of exercise, the bronchi of both non-asthmatic
and asthmatic individuals dilate; however, after several minutes non-asthmatic bronchi remain well-dilated while asthmatic bronchi begin to constrict because of a series of reactions to airway cooling and dehydration of the airway surface liquid (Anderson & Holzer 2002).

Whereas extrinsic asthma is more common in children and is characterized by the immunochemical response to a perceived foreign threat, intrinsic asthma is more common in adults and is caused by physical hyperresponsiveness to hyperosmolarity in the airway. Osmolarity refers to the concentration of particles in a fluid (Anderson & Holzer 2002). As water evaporates from the airway surface, the relative concentration of particles (namely K+, Cl-, Na+, Ca++) increases (Anderson & Holzer 2002). This condition is known as hyperosmolarity, and the body tries to correct it by moving water from all local cells and by extravasating plasma. As water moves from cells to the surface tissue to hydrate the area, the donating cells become drier than normal. The result is an increase in the degranulation of local leukocytes such as mast cells living in the airways (Anderson & Holzer 2002). When the mast cells degranulate, they release histamines, leukotrienes, and other substances (Lieberman 1999). When these substances are released, from this point forward they trigger a chain of events that resemble the reaction extrinsic asthmatics described above. Likewise, the result of released histamines and leukotrienes is inflamed tissue, increased mucous production, and smooth muscle constriction, causing coughing, wheezing, and shortness of breath (Lieberman 1999).

The occurrence of EIB varies widely depending on the environment, since the primary contributing factors are coolness and dryness of the air (Anderson & Holzer 2002; Lieberman 1999). Naturally, cooler and drier air contributes to a higher risk of an
EIB-related asthmatic attack (Anderson & Holzer 2002; Lieberman 1999). Additionally, some exercises are more asthmagenic than others. Running is often considered the most asthmagenic, followed by cycling, and then, least of all, swimming (Lieberman 1999). Lieberman (1999) speculated that, although not completely known, the hierarchy of asthmagenic exercises is probably related to the rapidness of breathing contributing to dehydration as well as the humidity of the environment. In other words, because swimming occurs in an aquatic environment, the air is more humidified. As far as running being more asthmagenic than cycling, the likely explanation is that running is more physically demanding on the body than cycling and involves the movement of all extremities, which increases the metabolic and breathing rates.

However, having EIB does not preclude an individual from exercising and having an active lifestyle (Rundell et al. 2002). Many premiere athletes are known to suffer from EIB, but are able to manage it well enough to still compete at the most physically demanding levels (Rundell et al. 2002; Wilber 2002). Managing EIB can involve taking a bronchodilator 15 to 30 minutes before exercising (ATS 2008) as well as controlling the environment whenever possible to exercise in warmer, more humidified air.

2.3 Exhaled Nitric Oxide in Extrinsic and Intrinsic Asthma

In both extrinsic and intrinsic asthmatic reactions, nitric oxide production is often elevated and triggers vasodilation and increased blood flow (Barnes & Kharitonov 1996). It is associated with eosinophilic inflammation rather than other types of inflamed cells (Dweik et al. 2011). Nitric oxide (NO) is a gaseous mediator and potent vasodilator which plays an important signaling role in airway physiology and the pathophysiology of airway diseases (Barnes & Kharitonov 1996). Endogenous NO is synthesized from the
amino acid l-arginine by the enzyme NO synthase (NOS) (Sapienza et al. 1998). There are three different types of NOS: constitutive (cNOS), inducible calcium-independent enzyme (iNOS), and endothelial (eNOS). When NO is produced in small amounts by cNOS, it may be beneficial in relaxing smooth muscles in the airways; however, in large doses produced by iNOS, NO is harmful and indicative of inflammation (Sapienza et al. 1998).

In the early 1990s, it became widely known that NO was linked to inflammation and soon afterwards the Swedish researchers Gustafsson and Alving demonstrated that fractional concentration of exhaled NO (FeNO), measured in parts per billion (ppb), could be used as a marker for airway inflammation (Rickard 2012). While FeNO concentration is an indicator of a variety of airway issues, including bronchiectasis, vascular disease, and nasal disease (Barnes & Kharitonov 1996), its clinical application has been mostly explored in asthma (Rickard 2012). In normal individuals, FeNO concentration levels reach up to 50 ppb for adults and up to 35 ppb for children, while individuals with non-stable asthma often have FeNO levels in excessive of 50 ppb for adults and 35 for children (Dweik et al. 2011). The ATS recommends using 47 ppb as the clinical cut point for determining steroid responsiveness for treatment purposes (Dweik et al. 2011).

FeNO levels may be measured in a variety of ways, including the current standard of chemiluminescence analyzers and the most accurate but least convenient method of chromatography-mass spectrometry (Barnes & Khartinov 1996). Most recently, a method of measuring FeNO using electrochemical sensors in a handheld, lightweight, and more affordable device called the NIOX® MINO has been introduced to the field. A few
studies have compared the reliability of the NIOX® device in comparison to chemiluminescence analyzers and found it acceptable for clinical application (Khalili, Boggs & Bahna 2007). According to the manufacturer’s website, the NIOX® has a 95% confidence interval of ±5 ppb (niox.org).

Although FeNO has been increasingly used as a marker for asthma, to our knowledge only one study so far has applied it to the study of the effects of training on asthmatic adults and two have applied it to studies on children. The results of these studies were contradictory in terms of the effect training has on FeNO, but these differences may be explained by the different age of the subjects, intensity of the exercise and/or severity of the asthma.

The two studies on children found no significant effect of training on FeNO levels (Bonsignore et al. 2008; Morreira et al. 2008). A study by Morreira et al. (2008) investigated the effect of training on 34 asthmatic children and found no change in FeNO, blood eosinophils or eosinophil cationic proteins. However, according to criticisms from Mendes et al. (2011), Morreira et al. failed to disclose the severity of asthma in the subjects, used the less accurate marker of blood eosinophils rather than sputum eosinophils and did not evaluate the anaerobic threshold parameters of the exercise. The other study by Bonsignore et al. (2008) assessed the effect on FeNO levels of exercise and a treatment of the leukotriene receptor antagonist montelukast (i.e. Singulair®) on 48 children with mild to moderate asthma, divided by half into a placebo and montelukast group. The placebo group showed no significant change in pulmonary function (FEV₁, FEV₁/FVC, FEF) and no significant change in FeNO concentration, although there were significant increases in cardiovascular function and workload (Max Workload, VO₂ AT,
VEMax, MaxHR). As Mendes et al. (2011) noted, though, Bonsiginore et al. is problematic because they did not precisely describe the progression in exercise training; only measured submaximal and not maximal aerobic threshold; and studied patients with mild rather than moderate or severe disease severity.

Unlike the previous two studies, Mendes et al. (2011) investigated the effects of aerobic training on the airway inflammation of adults with moderate to severe asthma using FeNO and induced sputum eosinophil cell count as the inflammation markers. The researchers assigned 51 subjects to either the control (n=24) or aerobic training group (n=27). Both groups participated in an educational program consisting of two classes for two hours each about asthma pathophysiology, medication skills, self-monitoring techniques, and environmental management strategies. Only the training group participated in the aerobic training program consisting of 30-minute sessions twice per week for three months. The program began with subjects exercising at 60% of VO₂ Max and increased to a 70% VO₂ Max. If the subject successfully completed two consecutive sessions at 70% VO₂ Max without symptoms, then the intensity was increased by 5% of heart rate until a maximal of 80% subject MaxHR (Mendes et al. 2011). Therefore, the intensity of the exercise began at moderate intensity and approached near-high intensity for some subjects.

The results of the study showed significant decreases in eosinophilic cell count, FeNO levels and asthma symptoms for the training group (Mendes et al. 2011). Moreover, the results were most significant for the most severe cases of asthma (Mendes et al. 2011). As a result of these findings, Mendes et al. (2011) suggested that the severity of asthma is an important factor in the effect exercise training has on FeNO levels.
Additionally, the intensity of the exercise may also be an important factor, as Mendes et al. have proposed.

2.4 Asthma Treatments

Asthma can be treated with exercise as well as pharmaceuticals. In most cases, asthma is treated with pharmaceuticals, which can be divided into two types: preventative treatments (so-called “controller” medications) and treatments during an attack (so-called “rescue” medications). Controller medications are taken daily to help control or maintain the degree of inflammatory mediator release in the airway, and include long-acting beta agonists (LABA), leukotriene modifiers, and corticosteroids (Persing 2010). Rescue medications should not be taken regularly except when needed, and include quick-relief, short-acting beta agonists (SABA) or anticholinergic bronchodilators (Persing 2010). In rare cases, long-term use and overuse of systemic corticosteroids among children is known to stunt growth, and for inhaled corticosteroids, findings of stunted growth were very mild and only occurred when the highest prescribed doses were used (Bartholow, Deshaies, Skoner & Skoner 2013; Florea, Gotia & Boldureanu 2012).

Non-pharmaceutical treatments include avoiding known triggers and regular exercise. However, with the omnipresence of many triggers, such as pollen as well as other pollutants and allergens, avoidance strategies are often not practical. Thus, exercise is one of the few non-pharmaceutical preventative treatments of asthma. To improve respiratory health, the ATS and European Respiratory Society (ERS) recommended that individuals with asthma exercise for 20 to 30 minutes at 60 to 75% of VO$_{2\text{max}}$ 2 to 5 days per week (Nici et al. 2006). The ATS stated that exercise is safe even for individuals with EIB as long as they take a SABA dose 15 minutes before exercise (Parsons et al.
2012). In a review of the literature, Lucas et al. (2005) concluded that exercise is an important component to pulmonary rehabilitation. Moreover, Shabaan et al. (2007) found that exercise decreased bronchial hyperresponsiveness among asthmatic adults.

2.4.1 Effect of Physical Activity on Children with Asthma

Among children, physical activity improves cardiovascular and exercise tolerance by increasing VO$_2$Max. In a review of eight studies with a total of 226 children, Ram et al. (1999) found exercise physical activity significantly increased VO$_2$Max in an aggregation of the data from all included studies. In a more recent review of the literature, Welsh et al. (2005) concluded that among 22 included studies, most found physical conditioning significantly improved VO$_2$Max. Possibly because of the increase in VO$_2$Max, exercise tolerance also improved. According to Welsh et al., training significantly increased the distance asthmatic children ran in 12 minutes.

While the effect of exercise on cardiovascular fitness is in agreement, the effect of physical activity on pulmonary function is still equivocal. Some studies on children with asthma have shown no improvement in pulmonary function post-intervention. Ram et al. (1999), in the same review of eight studies that found exercise improves cardiovascular function, found in contrast that an exercise interventions had no significant effect on resting lung function. However, a couple of studies have stated that physical activity has a positive effect on resting lung function. For instance, Fanelli (2007) found that among 38 Brazilian children with moderate to severe asthma, a 90-minute exercise regimen twice a week for 16 weeks significantly increased FEV$_1$ in the training group. Moreover, the intervention decreased the use of inhaled corticosteroids and decreased exercise-induced bronchoconstriction (EIB) and post-exercise breathlessness.
2.4.2 Effect of Physical Activity on Adults with Asthma

In terms of cardiovascular fitness, exercise tolerance, and pulmonary function, the findings regarding the effect of exercise on adults with asthma are similar to children. Virtually all studies showed improvement in cardiovascular fitness and exercise tolerance. In a foundational study in the field of exercise interventions for asthmatic adults, Cochrane and Clark (1990) found highly significant improvements in VO$_2$ Max and Max O$_2$ pulse among 36 adult subjects aged 16-40. Another early study found peak O$_2$ consumption increased by 15% and heart rate increased by 30% (Haas et al. 1987). More recent studies have reinforced these findings as well. According to a summary of three literature reviews on the topic of exercise conditioning for patients with asthma conducted by Lucas et al. (2005), almost all clinical studies showed improvement in cardiovascular fitness and exercise performance (Orenstein 2002; Satta 2000; Clark 1993). Likewise, Mendes et al. (2011) found increase in VO$_2$ Max as well. Again, as was found in children, the increase in cardiovascular fitness was found in parallel with an increase in exercise tolerance, such as Cochrane and Clark’s finding of a highly significant improvement in anaerobic threshold (Cochrane & Clark 1990).

However, the results of physical training on pulmonary function in adults with asthma are still questionable. Among three literature review, some studies showed a slight but significant improvement in pulmonary function in terms of FEV$_1$ and PEF between pre- and post-intervention, but the majority has found no significant improvement (Lucas et al. 2005; Cochrane & Clark 1990). Moreover, some aspects of pulmonary function have been shown to improve even when FEV$_1$ did not. For example, Mendes et al. (2011) found when comparing between 68 adult subjects divided half into a
control group and half into a training group, among the training group, the intervention significantly improved asthma free days and lowered the asthma exacerbation; however, in the same sample, training did not significantly affect FEV\textsubscript{1} (Mendes et al. 2011). Similarly, Haas et al. (1987) found on one hand that training did not improve pulmonary function in terms of FEV\textsubscript{1} and FVC, but on the other hand it did increase in maximum voluntary ventilation (MVV).

Chandratileke et al. (2012) conducted a meta-analysis of 19 studies (695 participants) on the topic of physical training for asthmatic adults and children. Many of these included studies were summarized above, but the Cochrane review meta-analyzed the data, making the findings more statistically powerful. The results pooled data on the following measures: $V_{E_{\text{max}}}$ (4 studies; 111 subjects); $V_{O_{2, \text{max}}}$ (6 studies; 149 subjects); $H_{R_{\text{max}}}$ (2 studies; 34 subjects); FEV\textsubscript{1} (6 studies; 204 subjects); FVC (4 studies; 122 subjects) (Chandratileke et al. 2012).

Overall, the pooled data revealed physical training significantly improved cardiovascular fitness and work capacity. Physical training significantly increased $V_{E_{\text{max}}}$, $V_{O_{2, \text{max}}}$, and $H_{R_{\text{max}}}$ (Chandratileke et al. 2012). The combined data for work capacity was less conclusive because the data could not be statistically pooled as a result of differing measures. Two of these studies on work capacity showed statistically and clinically significant increases in work capacity (Ahmaidi et al. 1993; Matsumoto et al. 1999), while one did not (Van Veldhoven 2001). However, the one study finding no increase in work capacity did not adequately report its methods, so it is difficult to determine why its results differed (Chandratileke et al. 2012). Finally one study (Turner 2010) found 6-minute walking distance (MWD) was longer for the 20 asthmatic subjects
who participated in an exercise intervention than 15 control subjects, but the results were not statistically significant.

In contrast, the pooled data found no significant change in resting lung function in and pulmonary function measures. Specifically, no significant change was found in PEF, FEV₁, or FVC. As a noteworthy point, though, the meta-analysis found physical training was tolerated with no reported adverse effects. Moreover, none of the studies mentioned worsening of asthma following training, supporting the safety for these types of exercise interventions for asthmatic adults and children.

2.5 Intensity of Exercise and Asthma

Most of the studies above do not mention the intensity of the exercise interventions the investigators used, but based on the description of the methods, they fall within the moderate intensity range. The following two studies explicitly identify the intensity of the intervention, one of which is moderate and the other high intensity. In their pilot study, Boyd et al. 2012 defined moderate-intensity exercise as 60-75% of maximum heart rate (HRmax). Following a 12-week moderate exercise program consisting of aerobic walking three times per week given to eight adults, the Boyd et al. noted trend towards improved fitness level. Specifically, VO₂ Max and total treadmill time significantly increased pre- and post-intervention in the exercise group (Boyd et al. 2012). However, like all of the above studies, the researchers found no change in lung function (FEV₁, FEV₁/FVC ratio) (Boyd et al. 2012).

Apparently only three studies have investigated the effect of HIIT on the cardiovascular fitness, exercise tolerance, and pulmonary function of asthmatic subjects, all of them with the same lead investigator. In the original study, Emtner et al. (1996)
defined HIIT as reaching as 80-90% of predicted maximal heart rate determined from the results of maximal and submaximal ergometric cycling tests. The study subjected 26 adults with mild to moderate asthma to a 10-week HIIT program in a swimming pool, including a 12-min warm-up period followed by five intervals of 2-minute high-intensity exercises separated by 1½-min periods of mild exercise (16 min total), and then 7 minutes of cooling down followed by 10 minutes of stretching (Emtner et al. 1996). Pre- and post-test results showed mean heart rate significantly decreased (Emtner et al. 1996). Moreover, walking distance increased significantly and perceived exertion significantly decreased (Emtner et al. 1996). Unlike the other studies which were largely moderate intensity, Emtner et al. found a significant increase in mean FEV₁ and forced expiratory flow (FEF) as a result of their HIIT intervention. With only three studies on the effect of HIIT on asthmatic patients, all of which were conducted nearly 20 years ago, it is not clear at this point if the positive results for pulmonary function are correlated with the high-intensity of the exercise intervention or if they are coincidental results. Follow-up studies by Emtner (1998a; 1998b) showed the positive results persisted three years later and the findings were similar between both water-based and land-based HIIT protocols.

2.6 Safety of HIIT

HIIT has been shown to improve pulmonary function in healthy subjects just as well as ET, but in a more time-efficient manner (Dunham & Hams 2012). However, HIIT may not be appropriate in all cases because it may pose a health risk to push some subjects with chronic diseases to high-intensity levels of exercise. Despite this possible risk, most studies have shown HIIT is safe for a variety of chronic diseases. Normandin et al. (2013) showed HIIT is well tolerated and even beneficial for congestive heart
failure patients who are young males with few comorbidities. Likewise for patients with type 2 diabetes, HIIT was shown to be a safe and effective treatment (Gillen et al. 2012). HIIT has also been shown to be safe and effective for overweight young males while also decreasing fat and increasing muscle mass (Heydari, Freund & Boutcher 2012). Because of findings such as these and others, Shiraev and Barclay (2012) concluded that HIIT is both safe and effective for patients with diabetes, stable angina, heart failure and post-myocardial infarct.

As for asthma, the evidence regarding the safety of HIIT is not as well-researched, but in the few studies that have applied HIIT to asthmatic subjects, the protocol appears to be safe. Emtner has conducted three separate studies on the effects of HIIT on asthmatic adults: one using HIIT in the water (Emtner et al. 1996), one following up with the first study three years later (Emtner et al. 1998a), and one comparing the differences between HIIT on land and in water (Emtner et al. 1998b). All three studies reported HIIT is safe and effective for asthmatics.

In the first study, Emtner et al. (1996) submitted asthmatic 26 subjects to HIIT aquatic exercises. None of the subjects were injured and all were able to maintain the very high intensity without asthma symptoms. Not only was HIIT safe for these asthmatic subjects, but the researchers showed the intervention improved both cardiovascular fitness and, unlike non-HIIT studies, pulmonary function (Emtner et al. 1996). Following up three years later, Emtner et al. (1998a) found that no negative health outcomes occurred after the initial HIIT intervention, and a subgroup of subjects who continued with moderate exercise at least once or twice per week over the next three years (n=26; 45% of the original intervention group) reported significantly fewer emergency room
visits and fewer asthmatic symptoms than before the intervention. In Emtner et al. (1998b), the researchers compared the effects of land-based and water-based HIIT on inactive asthmatic adults and found both were effective and safe. In both groups, no asthmatic attacks occurred in connection with the training sessions, while cardiovascular condition improved significantly and similarly. Likewise, the number of subjects who reported experiencing exercise induced bronchoconstriction (EIB) decreased from five to two in the water HIIT group and from five to one in the land HIIT group after the 10-week intervention.

Moreover, the ATS and ERS stated exercise for asthmatics is safe, and has highly recommended that individuals with asthma exercise at 60 to 75% of VO$_{2\text{max}}$ two to five days per week for 20 to 30 minutes (Nici et al. 2006). While EIB may add to the risk of negative reactions to exercise among asthmatics, the ATS released a statement that exercise is completely safe for those with EIB as long as they take a bronchodilator 15 to 30 minutes before exercising (Parsons et al. 2013).

2.7 Conclusion

The role of the adaptive immune system and the effect of environmental exposure (or lack thereof) supports the use of non-pharmaceutical interventions such as exercise training that increase the variety of exposure and help build a more robust and resistant adaptive immune system from within. If the immune systems of some children who live in environments characterized by largely harmless pollutants more than threatening parasites and bacteria are underdeveloped and oversensitive, leading to increased occurrence of asthma, then using pharmaceuticals to treat the condition does nothing to change interaction between the environmental exposure and the underdeveloped immune
system that underlies the condition except to create dependence on the medication. In contrast, exercise potentially exposes the body to a variety of environments (including the various particles and agents in such environments) as well as strengthening the body from within. Theoretically, exercise has the potential to help develop a more robust immune system through increased interaction and activity between the body and its environment, while pharmaceuticals potentially promote the body to become dependent on medication to solve the problem for it.

In general, most studies on the effect of exercise on asthma have focused on children as the subject, perhaps because of the rehabilitative potential and value of exercises for younger people compared to adults. Additionally, most studies used moderate-intensity exercises as the intervention. As of the time of this thesis, only three studies have investigated the effect of HIIT on asthmatic adults, were conducted using aquatic exercises, and are somewhat outdated (Emtner et al. 1996, 1998a, 1998b). Therefore, no previous studies have explored the impact of non-aquatic HIIT on adults with asthma.

Collectively, the studies have shown exercise to be clearly and significantly beneficial to cardiovascular fitness and exercise tolerance for both children and adults with asthma. Although most of the studies found that exercise interventions had no significant effect on most measures of pulmonary function, one of the studies that did find a positive and significant effect on pulmonary function used HIIT protocol for its intervention, leading to the question of whether the exercise intensity is an important factor. Likewise, the severity of asthma also appears to be important in relation to the therapeutic effect of exercise, suggesting the effect is greater for more severe cases.
While the most common measures in studies investigating the effect of exercise on asthmatic individuals have been cardiovascular ($\text{VO}_2\text{Max}$) and pulmonary (FEV$_1$, FEV$_1$/FVC ratio, & PEF), a few studies have started to measure FeNO as its reliability as a marker for asthma has been increasingly demonstrated. Only one such study using FeNO as a marker has studied adults with asthma, so the literature is currently sparse in that area.

Given the current literature, it is clear there is a gap in what is known about the effect of non-aquatic HIIT interventions on lung inflammation as measured by FeNO, as well as on cardiovascular fitness, exercise tolerance, and pulmonary function among adults with asthma. Thus, the literature leads to the following research question: does HIIT reduce lung inflammation and improve pulmonary function and cardiovascular fitness among adults with asthma?
Chapter 3

Methodology

This chapter explains the methodological details of the study, including subjects, instrumentation, data collection procedures, and data analysis procedures. These methods were designed to answer the research question: does high intensity interval training (HIIT) reduce lung inflammation and improve pulmonary function and cardiovascular fitness among adults with asthma? The methods also aimed to answer the sub-question: does HIIT improve exercise tolerance in adults with asthma?

3.1 Subjects

Subjects included two groups: healthy subjects and asthmatic subjects. Fifteen healthy (non-asthmatic) subjects male adults aged 18-45 years were targeted. The asthmatic group also targeted 15 male subjects, 18-45 years old. The sampling method was purposive, non-random sampling. Subjects for both groups were recruited using flyers throughout the campus and class visits. Both groups excluded subjects who fit any of the following criteria: cardiovascular disease patients, smokers, people with cardiopulmonary diseases besides asthma, and active asthmatics. Active asthmatics were defined as those who do cardiovascular exercise routines (swimming, biking, running, jogging, etc.) at least three times per week for at least 20 minutes per workout. If the
asthmatic subject was less active than this definition, then they were considered sedentary
are were included in the study.

3.2 Instrumentation

Demographic (age, sex, and ethnicity) and anthropometric (height and weight)
data were gathered as background information for both asthmatic and healthy groups.
Additionally, as detailed below, three pulmonary measures, one lung inflammation
measure, two ventilation measures, and three exercise tolerance measures were collected.
Finally, a researcher-designed, self-report, comfort-level questionnaire was used to gather
the attitudes of the subjects. All of these measures were collected at both pre- and post-
HIIT intervention stages except demographic data, which was only collected once at the
beginning of the study.

3.2.1 Pulmonary Measures

Pulmonary data on the subjects were collected using the following measures:

- Peak expiratory flow (PEF) was measured by peak flow meter. This instrument
  measures the maximum speed of expiration and requires the subject to take a
deep inspiratory breath, and then exhale deep and forcefully into the instrument.

- Forced vital capacity (FVC) was measured by the Micro1 Spirometer (MD Spiro
  and Micro Direct, Inc.; Lewiston, ME). FVC is the total volume of air that can be
forcibly blown after full inspiration.

- Forced expiratory volume in one second (FEV$_1$) was measured by the Micro1
  Spirometer. FEV$_1$ is defined as the volume of air that is forcibly blown out in the
first second of a FVC maneuver. The Micro1 Spirometer automatically measures
both FEV\textsubscript{1} and FVC in one breath. From these measures, the FEV\textsubscript{1}/FVC ratio was calculated.

### 3.2.2 Fractional Concentration of Exhaled Nitric Oxide

As an indicator of lung inflammation levels, fractional concentration of exhaled nitric oxide (FeNO) was used. FeNO was collected using the NIOX MINO® (09-1000) device (Aerocrine; AB.SE-17173; Solna, Sweden). This device measures the concentration of NO in the breath in terms of parts per billion (ppb).

### 3.2.3 Ventilation Measures

To measure the amount of ventilation occurring among the subjects, we used minute ventilation (VE) and CO\textsubscript{2} production (VCO\textsubscript{2}). A metabolic cart was used to collect the VE and VCO\textsubscript{2} data, which is a system comprising a computer, monitor, breathing tubes, and a mouthpiece.

### 3.2.4 Exercise Tolerance Measures

The exercise tolerance data of the study was collected using VO\textsubscript{2 Max} test, time to exhaustion (TTE), and peak work rate (PWR). The VO\textsubscript{2 Max} test involved ergometric cycling with the subject warm up for 4 minutes on 20 watts on a stationary bike, then on an incline at 20 watts increasing by 20 watts per minute until exhaustion. Given the time the subject is able to work until exhaustion, their VO\textsubscript{2 Max}, TTE, and PWR were measured using the metabolic cart. TTE was also measured by the researcher using a standard stopwatch to ensure accuracy. The data were also used to calculate the intensity for the rest of the HIIT protocol, which was set at 75% peak output (PO). The following formula was used to calculate 75% PO:

\[
75\% \ PO = (20 \text{ watts} + t \ast [20 \text{ watts}]) \ast .75
\]
where \( t \) = the exercise time after the warm-up.

### 3.2.5 Comfort-Level Questionnaire

To determine the asthmatic subjects’ comfort levels and attitudes towards the HIIT intervention, a 10-item, researcher-developed, self-report questionnaire on a four-point Likert-type scale called the Comfort Level Questionnaire was developed (see Appendix). The first four items of the questionnaire were worded in positive terms, so agreement indicates a positive attitude towards exercise. In contrast, the next six items were worded negatively, so agreement indicates a negative attitude towards exercise. No reliability tests were used to assess this questionnaire. The questionnaire was first administered to the asthmatic subjects on the second day of the study after the VO2 Max test and again on the final day of the study after the sessions of the protocol were completed and measurements were taken.

### 3.3 Data Collection Procedures

The candidates for the study were brought to the Cardiopulmonary and Metabolism Research Laboratory at The University of Toledo and received a summary and explanation of the procedures. Following the overview of the procedures, those willing to participate signed a consent form. First, the demographic and anthropometric data were gathered, followed by the participating subjects’ vital signs, which included heart rate, blood pressure, and respiratory rate. The schedule of the study was divided into three stages: pre-intervention, intervention, and post-intervention, which took a total of 4-weeks (see Table 3.1).
Table 3.1: Schedule of Intervention Procedures

<table>
<thead>
<tr>
<th>Mon.</th>
<th>Week #1</th>
<th>Week #2</th>
<th>Week #3</th>
<th>Week #4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consent Form</td>
<td>HIIT at 75% PO¹</td>
<td>HIIT at 75% PO</td>
<td>Pulmonary Function</td>
</tr>
<tr>
<td></td>
<td>Health Qs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anthropometric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wed.</td>
<td>Nitric oxide Test</td>
<td>HIIT at 75% PO</td>
<td>HIIT at 75% PO</td>
<td>Nitric oxide Test</td>
</tr>
<tr>
<td>Fri.</td>
<td>VO₂ Max Test</td>
<td>HIIT at 75% PO</td>
<td>HIIT at 75% PO</td>
<td>VO₂ Max Test</td>
</tr>
</tbody>
</table>

¹ Peak Power Output

3.3.1 Pre-intervention

The pre-intervention occurred over a span of two separate meetings. On the first day of the study, all pulmonary function tests (FEV₁, FEV₁/FVC ratio, and PEF) were conducted on all subjects three times each and the highest outcome were used. For the asthmatic patients, FeNO were also collected on the same day as the pulmonary function tests. The FeNO were collected just once using the NIOX MINO® device by having the subjects empty their lungs, inhale slowly through a filter attached to the device and exhale slowly through the same filter until the alarm goes off. After 90 seconds, the NIOX MINO® device produces the FeNO measure in terms of ppb. For the asthmatic group, the above tests were conducted after 12 hours of abstaining from administration of any type of corticosteroids to avoid confounding factors that might decrease the FeNO levels (Dweik et al. 2011).

On the second day, the same FeNO test were conducted for the healthy subjects along with the VO₂ Max test. However, for the asthmatic subjects, only the VO₂ Max test were conducted on the second day because they were instructed to use a bronchodilator...
that would interfere with the FeNO test and pulmonary function measurements. For the VO\textsubscript{2}\text{Max} test, the subjects warmed up for 8 minutes on 20 watts on a stationary bike and then exercised on an incline at increasing resistance 20 watts/minute until exhaustion.

### 3.3.2 Intervention Protocol: High Intensity Interval Training

The exercise intervention protocol involved an 8-minute warm-up, followed by a 20-min, high-intensity, ergometric cycling workout in 60-second on-and-off intervals every other day, and ending with a 5-minute cool down (see Figure 1). The subjects followed this protocol three days a week for two weeks. The protocol is designed to push patients to only 75% VO\textsubscript{2}\text{Max} levels based on the subjects’ maximum capacity from the first day. According to the guidelines of the ATS, 60-75% of the maximum work rate is a recommended healthy workout range for asthmatic subjects (Boyd et al. 2012). Additionally, all subjects were instructed to use bronchodilators before training and, if necessary, throughout the training intervention.

![Figure 3.1: High Intensity Interval Training Intervention Protocol](image)

Figure 3.1: High Intensity Interval Training Intervention Protocol
3.3.3 Post-intervention

The post-intervention involved administering the same pulmonary function measures, FeNO test, and VO$_2$Max test as the pre-intervention. Similar to the pre-intervention, the healthy subjects were submitted to the pulmonary function tests on the first post-intervention day (Day 9) and the FeNO and VO$_2$Max test on the second post-intervention day (Day 10). Likewise, asthmatic subjects went through the pulmonary function and FeNO tests on the first post-intervention visit (Day 9), followed by the VO$_2$Max test on the second day (Day 10). For the pulmonary function measures and FeNO tests, the asthmatic patients were instructed to abstain from using any bronchodilator for 12-hours prior to the tests, but were instructed to use a bronchodilator before the VO$_2$Max test.

3.4 Data Analysis Procedures

Data were analyzed using SPSS version 21.0 statistical software (IBM; Chicago, IL). The two-way repeated measures ANOVA were conducted to compare the pre- and post-intervention mean scores in the pulmonary function tests (FEV$_1$, FEV$_1$/FVC ratio, and PEF), FeNO concentration levels, and VO$_2$Max in the asthmatic group and healthy group. Furthermore, Student-Newman-Keuls Method post hoc analyses were conducted focusing on factors that showed significant differences in the two-way ANOVA, in which additional specification of the differences among means is needed.
Chapter 4

Results

This chapter reports the results of the data analysis for the HIIT intervention protocol described in the previous chapter. The findings are divided into demographics, healthy pre- and post-intervention results, asthmatic EIB pre- and post-intervention results, asthmatic pre- and post-intervention non-EIB results, and asthmatic versus healthy results.

4.1 Demographics

The demographics here are presented as descriptive statistics and provide a background regarding the types and numbers of subjects of different ages, ethnicities, genders, and lifestyles.

4.1.1 Healthy Subjects

At first, the healthy group consisted of 15 male subjects and no females. However, because the final number of asthmatic subjects only totaled seven, data from the first seven healthy subjects who underwent the protocol were used for analysis purposes. Among final seven subjects in the healthy group, the mean age was $22.6 \pm 3.4$. All were non-smokers, moderately active, and had no asthma symptoms. The average weight of the healthy group was $75.6 \pm 12.3$ kg and the average height was $175.8 \pm 6.5$
cm. One participant was a native Cameroonian, another was a native Russian, and the rest were Caucasian Americans.

4.1.2 Asthmatic Subjects

The asthmatic group originally consisted of eight male subjects and no females; however, one subject withdrew from the study after complaining about the protocol and leg pain after five minutes of cycling (N=7). All but one suffered from EIB and all reported having mild to moderate symptoms. All reported being non-smokers and sedentary, participating in extended physical activity fewer than once per week. The mean age for the asthmatic group was 25.9 ± 5.1. The mean height was 174.4 ± 7.5 cm and the mean weight was 79.8 ± 17.1 kg. See Table 4.1 for a summary of the subjects’ demographic variables.

<table>
<thead>
<tr>
<th>Group</th>
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<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Gender</th>
</tr>
</thead>
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<td></td>
<td></td>
</tr>
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<td>180</td>
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<tr>
<td>Subject 2</td>
<td>33</td>
<td>178</td>
<td>104.5</td>
<td>M</td>
</tr>
<tr>
<td>Subject 3</td>
<td>22</td>
<td>172</td>
<td>83.2</td>
<td>M</td>
</tr>
<tr>
<td>Subject 4</td>
<td>32</td>
<td>160</td>
<td>60.9</td>
<td>M</td>
</tr>
<tr>
<td>Subject 5</td>
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<td>175</td>
<td>96.4</td>
<td>M</td>
</tr>
<tr>
<td>Subject 6</td>
<td>21</td>
<td>183</td>
<td>60</td>
<td>M</td>
</tr>
<tr>
<td>Subject 7</td>
<td>21</td>
<td>173</td>
<td>70.5</td>
<td>M</td>
</tr>
<tr>
<td>Mean</td>
<td>25.9</td>
<td>174.4</td>
<td>79.8</td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject 1</td>
<td>29</td>
<td>172.5</td>
<td>57.7</td>
<td>M</td>
</tr>
<tr>
<td>Subject 2</td>
<td>25</td>
<td>177.8</td>
<td>81.4</td>
<td>M</td>
</tr>
<tr>
<td>Subject 3</td>
<td>21</td>
<td>169</td>
<td>72</td>
<td>M</td>
</tr>
<tr>
<td>Subject 4</td>
<td>22</td>
<td>169</td>
<td>85.6</td>
<td>M</td>
</tr>
<tr>
<td>Subject 5</td>
<td>19</td>
<td>174.5</td>
<td>68.2</td>
<td>M</td>
</tr>
<tr>
<td>Subject 6</td>
<td>21</td>
<td>188</td>
<td>70</td>
<td>M</td>
</tr>
<tr>
<td>Subject 7</td>
<td>21</td>
<td>180</td>
<td>94.6</td>
<td>M</td>
</tr>
<tr>
<td>Mean</td>
<td>22.6</td>
<td>175.8</td>
<td>75.6</td>
<td></td>
</tr>
</tbody>
</table>
4.2 ANOVA Analysis Results

To address whether the protocol had any effect on the subjects’ cardiovascular fitness, pulmonary health, and FeNO levels, a two-way ANOVA test was used for each measure. Afterwards, a post-hoc analysis was used to further distinguish differences among means. The results are reported for each of the measures.

4.2.1 Pulmonary Function Tests

There were no significant differences between groups in any of the pulmonary function tests: FEV₁/FVC (p=0.20), FVC (p=0.07), and PEF (p=0.78). The mean values for FVC and FEV₁/FVC for the healthy group were 94% and 99% of both the pre- and post-HIIT predicted value respectively, which put them in the normal range. The percent predicted among the asthmatic group for FVC (79% pre-HIIT; 81% post-HIIT) and FEV₁/FVC ratio (104% pre-HIIT; 107% post-HIIT) put the asthmatic group in the mild asthmatic range. The two-way repeated measures ANOVA showed no significant difference pre- and post-intervention measures among both groups for FVC (p=0.36), FEV₁/FVC ratio (p=0.27), and PEF (p=0.42). Thus, overall no significant effect of the intervention was found on any of the pulmonary function measures among both the asthmatic and the healthy subjects.

4.2.2 Fractional Exhaled Nitric Oxide

There was a significant difference between the healthy and asthmatic group in the concentration of FeNO levels (p = 0.002). The mean FeNO level for the healthy group was 17 ± 2 ppb while the mean for the asthmatic group was 28 ± 2 ppb. The two-way repeated ANOVA of the FeNO test on the healthy indicated no significant reduction in the fractional exhaled concentration of nitric oxide (p=0.68). Similarly, no significant
difference within the asthmatic group was found. Therefore, this two-week HIIT protocol had no significant effect on the level of lung inflammation.

Figure 4.1: The effect of two weeks of HIIT on FeNO in Asthmatic (N=7) and Healthy (N=7) subjects.

*: Significant difference between HIIT-A and HIIT-H (P<0.05).
Data was represented by mean ± SD.
Table 4.2: Summary of the effect of HIIT. Below are the means of all measures pre- and post-HIIT for both Asthmatic (N=7) and Healthy (N=7) subjects with indications of significance.

<table>
<thead>
<tr>
<th></th>
<th>Asthmatic</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>161 ± 5.6</td>
<td>173 ± 5.1$\text{§}$</td>
</tr>
<tr>
<td>PEF (L/m)</td>
<td>556 ± 25</td>
<td>561 ± 23</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>4.167 ± 0.3</td>
<td>4.294 ± 0.3</td>
</tr>
<tr>
<td>% predicted</td>
<td>79 %</td>
<td>81 %</td>
</tr>
<tr>
<td>FEV₁(L)</td>
<td>3.6 ± 0.3</td>
<td>3.8 ± 0.3</td>
</tr>
<tr>
<td>% predicted</td>
<td>82%</td>
<td>86%</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.87 ± 0.03</td>
<td>0.89 ± 0.03</td>
</tr>
<tr>
<td>% predicted</td>
<td>104 %</td>
<td>107 %</td>
</tr>
<tr>
<td>VO₂ Max (L/m)</td>
<td>2.45 ± 0.1$\ast$</td>
<td>2.67 ± 0.2$\ast$</td>
</tr>
<tr>
<td>TTE (sec)</td>
<td>691 ± 40$\ast$$\dagger$</td>
<td>781 ± 41$\ast$$\dagger$</td>
</tr>
<tr>
<td>PWR (watts)</td>
<td>175 ± 13$\ast$$\dagger$</td>
<td>203 ± 14$\ast$$\dagger$</td>
</tr>
<tr>
<td>VCO₂ (L/m)</td>
<td>2.72 ± 0.2$\ast$</td>
<td>3.27 ± 0.2$\ast$$\dagger$</td>
</tr>
<tr>
<td>VE (L/m)</td>
<td>77.77 ± 7.9$\ast$</td>
<td>95.81 ± 6.6$\ast$</td>
</tr>
<tr>
<td>FeNO (ppb)</td>
<td>28 ± 2$\ast$</td>
<td>28 ± 2$\ast$</td>
</tr>
</tbody>
</table>

$\ast$ Significant difference between groups (ANOVA)
$\dagger$ Significant difference between times (ANOVA)
$\ddagger$ Significant difference between group X time (ANOVA)
$\S$ Significant difference within group over time (post-hoc analysis)
4.2.3 Ventilation

The groups differed significantly in minute ventilation (VE) (p=0.002) and VCO₂ (p<0.001). The mean value for the VE among the healthy was 136.04 ± 8.93 L/min. The mean value for the VE among the asthmatics was 86.80 ± 8.93 L/min. The average VCO₂ among the healthy group including pre- and post- measures was 4.53 ± 0.19. The average VCO₂ among the asthmatic group was 2.99 ± 0.19.

![VE Graph]

Figure 4.2: The effect of two weeks of HIIT on peak VE in Asthmatic (N=7) and Healthy (N=7) subjects.
*: Significant difference between HIIT-A and HIIT-H (P<0.05).
Data was represented by mean ± SD.

The ANOVA showed no significant difference in VCO2 in the time variable (pre- and post-HIIT for both groups), but it did reveal a significance in the interaction of group X time (p=0.049). A Student-Newman-Keuls Method showed that there was a significant difference pre- and post-HIIT among the asthmatic group (p=0.021), but no difference
occurred in the healthy group. The mean VCO2 value for the asthmatic group pre-
intervention was $2.72 \pm 0.15$ L/min while the mean value post-intervention was $3.27 \pm 0.15$ L/min.

![VCO2 Graph](image)

Figure 4.3: The effect of two weeks of HIIT on peak VCO2 in Asthmatic (N=7) and
Healthy (N=7) subjects.

*: Significant difference between HIIT-A and HIIT-H (P<0.05).
#: Significant difference between pre- and post-HIIT (P<0.05).

Data was represented by mean ± SD.

4.2.4 Exercise Tolerance

Between the groups, a significant difference was found in their VO2Max measures
(p <0.001). The mean value for the VO2Max among the healthy was $3.80 \pm 0.17$ L/min.

The mean value for the VO2Max among the asthmatics was $2.56 \pm 0.17$ L/min. However,
no significant differences were found within the groups pre- and post-intervention.
The groups also differed significantly on time to exhaustion (TTE) (p <0.001). The average TTE among the healthy group including pre- and post- measures was 1015 ± 34 sec. The average TTE among the asthmatic group regardless of time was 735 ± 34 sec. The two-way repeated ANOVA revealed a significant difference over time pre- and post-HIIT with combined group measures (p<0.001) as well as in the interaction of group X time variables (p=0.029) in TTE. The Student-Newman-Keuls Method revealed a significant difference in TTE within both the asthmatic group (p<0.001) and the healthy (p=0.042), although the difference in the asthmatic group had greater significance. In the asthmatic group TTE, the mean value pre-intervention was 691 ± 11 s and the mean value...
post-intervention was 781 ± 11 s. In contrast, in the healthy group the mean TTE value pre intervention was 988 ± 11 s and the mean value post intervention was 1033 ± 11 s.

<table>
<thead>
<tr>
<th>Time to Exhaustion (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
</tr>
<tr>
<td>200</td>
</tr>
<tr>
<td>400</td>
</tr>
<tr>
<td>600</td>
</tr>
<tr>
<td>800</td>
</tr>
<tr>
<td>1000</td>
</tr>
<tr>
<td>1200</td>
</tr>
</tbody>
</table>

Figure 4.5: The effect of two weeks of HIIT on the time-to-exhaustion (TTE) in Asthmatic (N=7) and Healthy (N=7) subjects.

*: Significant difference between HIIT-A and HIIT-H (P<0.05).
#: Significant difference between pre- and post-HIIT (P<0.05).

Data was represented by mean ± SD.

Like the other two exercise tolerance measures, the groups differed significantly between each other in PWR (p<0.001). The average PWR among the healthy group were 296 ± 12 W, while the average PWR among the asthmatic group were 189 ± 12 W. The two-way repeated ANOVA of the PWR measure also showed a significant change over time pre- and post-HIIT with combined group measures (p<0.001) as well as in the interaction of group x time variables (p=0.029). The post-hoc analysis showed that both groups’ work output changed over time (asthmatic p<0.001; healthy p=0.024). The mean
PWR value pre-intervention in the asthmatic group was 175 ± 3 watts and the mean value post-intervention was 203 ± 3 W. In healthy group, the mean value for PWR pre-intervention was 290 ± 3 W and the mean value post-intervention was 302 ± 3 W. HIIT improved the exercise tolerance in both asthmatic and healthy groups.

Figure 4.6: The effect of two weeks of HIIT peak WR in Asthmatic (N=7) and Healthy (N=7) subjects.
*: Significant difference between HIIT-A and HIIT-H (P<0.05).
#: Significant difference between pre- and post-HIIT (P<0.05).
Data was represented by mean ± SD.

4.2.5 Heart Rate

Between the groups, no significant difference was found in their mean peak heart rates with combined pre- and post-HIIT values. However, a post-hoc analysis revealed a significant difference between the asthmatic and healthy groups pre-HIIT (p=0.017), but not post-HIIT. Analysis of the peak heart rate measures using the two-way repeated
ANOVA revealed a significant difference existed in the time variable (p=0.025) and in terms of group X time (p=0.004). The post-hoc analysis showed there was a significant difference within the asthmatic group pre- and post-HIIT (p=0.043), but not within the healthy group. The mean HR value for the asthmatic group pre-intervention was 161± 4 bpm and the mean value post-intervention was 173 ± 4 bpm. In contrast, there was no significant pre- and post- difference in heart rate in the healthy group.

![Heart Rate Graph](image)

Figure 4.7: The effect two weeks of HIIT on peak HR in Asthmatic (N=7) and Healthy (N=7) subjects.

*: Significant difference between pre-HIIT-A and pre-HIIT-H (P<0.05).
#: Significant difference between pre- and post-HIIT (P<0.05).
Data was represented by mean ± SD.
4.3 Questionnaire Results

By the end of the HIIT protocol, all of the asthmatic subjects reported agreeing more with the positive statements about exercise (Items 1, 2, 3, & 4) and disagreeing more with the negative ones (Items 5, 6, 7, 8, 9, & 10) in the Comfort Level Questionnaire. This indicates a slight improvement in their attitudes about exercise, although the small sample size made it impossible to determine the significance. At the beginning, the subjects strongly disagreed with Items 1-4, and the lowest score was for Item 3, which asked about confidence. In contrast, they strongly agreed with the negative statements (Items 5-10), and the highest level of agreement was Item 10 (“The nose clip and the mouth piece make me anxious”). The biggest change in attitude was found in the prompt about feeling confident about exercise (Item 3), which had an average of 1 (“Strongly Disagree) at the beginning and increased to 4 (“Strongly Agree”) by the end. This indicates the participants felt more comfortable by the end of the protocol.
Table 4.3: Results of the self-report comfort questionnaire. Below are the mean scores for each item in the questionnaire pre- and post-HIIT and the change over time. Scores are on a scale of 1 (“Strongly Disagree”) to 4 (“Strongly Agree”).

<table>
<thead>
<tr>
<th>Prompts</th>
<th>Mean Pre-HIIT</th>
<th>Mean Post-HIIT</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positively Worded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. My body is relaxed right now</td>
<td>2</td>
<td>4</td>
<td>+2</td>
</tr>
<tr>
<td>2. I want to exercise</td>
<td>2</td>
<td>4</td>
<td>+2</td>
</tr>
<tr>
<td>3. I feel confident about exercising</td>
<td>1</td>
<td>4</td>
<td>+3</td>
</tr>
<tr>
<td>4. I’m inspired to do my best</td>
<td>3</td>
<td>4</td>
<td>+1</td>
</tr>
<tr>
<td>Negatively Worded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. I’m afraid of exercising because of my condition</td>
<td>3</td>
<td>1</td>
<td>-2</td>
</tr>
<tr>
<td>6. I do not feel healthy right now</td>
<td>3</td>
<td>2</td>
<td>-1</td>
</tr>
<tr>
<td>7. I’m afraid of what is next</td>
<td>3</td>
<td>1</td>
<td>-2</td>
</tr>
<tr>
<td>8. I do not like it here</td>
<td>3</td>
<td>1</td>
<td>-2</td>
</tr>
<tr>
<td>9. I need to be better informed about my health</td>
<td>3</td>
<td>2</td>
<td>-1</td>
</tr>
<tr>
<td>10. The nose clip and the mouth piece make me anxious</td>
<td>4</td>
<td>1</td>
<td>-3</td>
</tr>
</tbody>
</table>

On a scale of 1-4, with 4 being strongly agree and 1 being strongly disagree
Chapter 5

Discussion

This chapter includes a discussion of the results and their broader significance in the field of exercise science and asthmatic research. In particular, the results of FeNO, pulmonary function, exercise tolerance, and HIIT safety are highlighted in relation to previous research. Additionally, the clinical implications, limitations, recommendations, and conclusions are discussed.

5.1 FeNO

The results of this study demonstrated a significant difference between the asthmatic and healthy groups in their FeNO levels. The significantly higher levels of FeNO among the asthmatic group aligns with findings in Buchvald et al. (2005), who found elevated FeNO levels among subjects with EIB. As stated in the sample demographics section of this thesis, all but one of the asthmatic subjects suffered from EIB. This is not unusual considering intrinsic asthma such as EIB is more common in adults than extrinsic asthma (Chen et al. 2012). Since the sample in this thesis mostly included subjects with EIB (86%), this result confirms previous research on the use of FeNO to diagnose EIB. However, according to the ATS recommendations on interpreting
FeNO levels, the mean value of the asthmatic group fell within the intermediate range, which the ATS recommended interpreting cautiously (Dweik et al. 2011). Although it should be interpreted cautiously, the difference between groups adds to the literature that FeNO levels can be a useful diagnostic and monitoring tool for asthma.

This study found no significant effect of exercise on FeNO levels pre- and post-HIIT. The ATS has stated that the change in FeNO levels after intervention is more valuable than any absolute value (Dweik et al. 2011). The lack of change in the FeNO levels among the asthmatic group pre- and post-HIIT means this particular protocol did not effectively reduce inflammation, but at the same time it did not exacerbate lung inflammation.

The lack of effect on FeNO agrees with findings from most of the literature except one study. Both Bonsignore et al. (2008) and Morreira et al. (2008) found no significant effect of training on FeNO levels on children, and Morreira found no effect on other measures of inflammation as well as (blood eosinophils and eosinophil cationic proteins). Bonsignore et al. found FeNO levels only decreased for a group treated with both exercise and an inhaled treatment, but not for an asthmatic group treated only with an exercise intervention. The only study that reported different results on the effect of exercise on FeNO levels among asthmatics was Mendes et al. (2011), who found significant decreases in eosinophilic cell count, FeNO levels, and asthma symptoms for the training group. However, the protocol for Mendes et al. was much longer than the current study (3 months compared to 2 weeks in this study), used aerobic training rather than HIIT, and included asthmatic subjects with more severe conditions. In fact, Mendes et al.
found the effect was strongest among the most severely asthmatic subjects. This suggests that duration of the protocol and severity of asthma are important variables in determining the effectiveness of exercise in reducing inflammation.

5.2 Pulmonary Function

The results of this thesis showed no significant difference between the healthy and asthmatic group in pulmonary function before or after the intervention. The lack of a difference suggests the asthmatic subjects kept their condition under good control and likely had low-to-moderate severity. As previous findings have shown, lower severity of asthma attenuates the effectiveness of exercise, particularly in terms of inflammation (Mendes et al., 2010). In other words, the more severe the condition, the greater effect exercise interventions seem to have. Alternatively, the lack of a significant difference between groups in pulmonary function could be the result of a small sample size.

5.3 Exercise Tolerance

This current study found a significant effect of HIIT training on most measures of exercise tolerance, including TTE and peak work rate but not VO2Max. In general, this aligns with previous studies on both children and adults, although most of them found significant effects on all measures of exercise tolerance including VO2Max (Chandratilleke et al. 2013; Ram et al. 1999; Welsh et al. 2005). Likewise, the non-medicated asthma group in Bonsignore et al. (2008) exhibited significant increases in cardiovascular function and workload (peak power work rate, VO2Max, VEMax, HRMax). The lack of a change in VO2Max could be attributed to the interaction of the brevity and intensity of the current protocol. Studies with similar protocol lengths (two weeks) but with higher...
intensity (supramaximal intensity) have demonstrated changes in VO$_{2\text{Max}}$ among healthy groups (Gibala et al. 2012), while studies with moderate intensity but longer protocol have demonstrated VO$_{2\text{Max}}$ changes among asthmatics (Chandratilleke et al. 2013). Thus, implementing either a longer protocol or higher intensity may make a difference. However, as Gibala et al. (2012) noted, supramaximal HIIT protocol are not safe for everyone, so may not be worth the risk to asthmatic patients. Still, even near-maximal HIIT protocol can be safe and effective if the protocol is longer. For instance, the only study to find a significant change in measures of pulmonary function among asthmatics pre- and post-intervention was Emtner et al. (1996), who used a higher intensity and longer duration of HIIT. Emtner defined HIIT as 80-90% Max HR and implemented the protocol at this intensity for 10 weeks.

5.4 HIIT Safety

This study demonstrated that HIIT is safe for both healthy people and asthmatics, since no asthma attacks, no difficulty breathing, and no physical collapse occurred. One of the asthmatic subjects did withdraw from the study after complaining about the nose and mouthpieces and leg pain after five minutes of cycling, but this seemed unrelated to asthma. Moreover, because FeNO levels remained stable, it appears the HIIT intervention did not worsen lung inflammation. The finding that the protocol was safe agrees with the literature, as none of the studies in Chandratilleke et al. (2013) mentioned worsening of asthma following training. However, Gibala et al. (2012) stated that while an extremely high intensity (supramaximal) may have a greater effect, they noted it may not be safe for all groups. Emtner et al. (1996) demonstrated an HIIT protocol as high as 90% Max HR
was safe for subjects with mild or moderate asthma. These findings suggest that a higher intensity than the current study can be safely implemented with asthmatic subjects, but perhaps not a supramaximal protocol.

5.5 Clinical Implications

One of the growing areas of research in asthma is the use of FeNO as a diagnostic tool. The current findings support the clinical use of FeNO since the healthy and asthmatic groups differed significantly on this measure. It appears FeNO can diagnose lung inflammation and distinguish between healthy and asthmatic, although the measures must still be interpreted cautiously. It is also possible that FeNO can help provide an additional definition of severity of asthma. Change in FeNO is especially useful, particularly for monitoring treatment compliance. In all clinical applications of FeNO, the recommendations and guidelines of the ATS for the use of FeNO as a diagnostic tool should be followed.

The findings of this study also have implications for the safety of HIIT. It is clear that HIIT was well-tolerated by the asthmatic subjects and so it can be implemented with low risk to asthmatic subjects. Even subjects with EIB did not have any adverse reactions to HIIT. Notably, HIIT did not worsen FeNO levels, suggesting no increased inflammation occurred. Moreover, the subjects reported being more comfortable with exercise by the end, so HIIT can potentially change attitudes towards exercise habits. With no adverse reactions and even increased comfort over time, these results suggest HIIT can be implemented to asthmatics without much risk.
Finally, this study reinforces early findings that exercise in general and HIIT specifically are effective interventions with little to no risk. It must be emphasized that current findings only support the use of HIIT as a potential therapy to prevent the worsening of asthmatic signs and symptoms; however, there is no evidence that it is a cure or an effective standalone treatment. Most likely, HIIT could be used in combination with pharmaceuticals to manage asthma without total dependence on medications.

5.6 Limitations

The major limitations of this study concerned the protocol and the sample. First of all, the protocol was probably too short. Two weeks is very brief and in most cases not long enough to see significant changes, especially only three times per week, although we did see some significant changes. Most previous studies on the effect of exercise on asthma have used protocol that last for at least six weeks and often even longer. The only studies that have shown significant changes over time among healthy groups used the super-high intensity seen in the Wingate method and other similar approaches, and no studies have attempted such an extreme intensity on at-risk populations. Likewise, the intensity of the HIIT protocol applied to the asthmatic group was probably lower than necessary. Strictly speaking, some may not even consider it high-intensity, although it is certainly was difficult for the subjects. The initial concern was for the safety of the asthmatic subjects, but with the findings showing no adverse reactions, a higher intensity was probably safe and could have been more effective.

The sample suffered from a few issues that likely limited the significance and generalizability of the findings. One issue is the small sample size. With only seven
asthmatic and seven healthy subjects, it prevented the use of t-tests to determine change over time on specific variables in each group. The small sample size also resulted in a large standard of error, which could have been reduced by a larger sample. A larger sample would also address a second issue, which was the mixing of intrinsic and extrinsic asthma. More asthmatic subjects can allow the asthmatic group to be divided into subgroups of intrinsic and extrinsic asthmatics. Without a large sample size, these groups were combined while the effect of exercise on each type might actually differ. A third limitation with the sample of asthmatics was the fact that all fell somewhere within the mild-to-moderate severity range, and none of the subjects fit the definition of severe asthma. Previous findings have shown that severity makes a difference on the effectiveness of exercise (more severe, greater the effect). Moreover, the low severity of the sample makes it not completely representative of the population of asthmatics that fit within the entire range of severity. A fourth and final limitation with the sample was the lack of females in either group. When it comes to physical traits, men and women differ greatly, so the findings of this study cannot be generalized to women.

5.7 Recommendations

Based on the findings and limitations, a few important future concerns and recommendations arise. What is most needed to build from the current study is an extension of the protocol and a higher intensity. The kind of physiological changes needed to make HIIT an effective treatment for asthma did not occur in a brief time period at 75% VO2Max, although either a longer duration or higher intensity, or both, could make a difference. All of the protocols in the previous literature have found
stronger results with either longer duration or higher intensity. At the time of designing this current study, safety was a concern for the treatment of the asthma group, so a somewhat lower intensity was chosen. However, the findings of this study in combination with previous literature shows a higher intensity can be safe. A supramaximal intensity such as the Wingate approach is probably still too risky for asthmatics, but below that level is likely safe. Thus, an intensity of 85-90% VO\textsubscript{2Max} is likely safe for asthmatics, although more research is needed in this area. It is also possible that such a study could produce more pronounced changes in FeNO levels not found in the current study because of brevity and lower intensity.

In addition to duration and intensity, severity of asthma seems to play a crucial role in how effective exercise interventions can be. In the current study, most of the asthmatic subjects appeared to only have mild asthma based on their pulmonary function measurements, while previous studies have found greater effects with more severe asthmatics. To help with accurately defining the severity of asthma and to determine the appropriate level of intensity based on the condition, future studies in this area should rely on thorough health records and physician consultation as much as possible. Doing so would avoid the problem of self-reported severity that can be affected by poor memory or ulterior motives of the subjects.

Future studies should also avoid mixing extrinsic with intrinsic asthmatics and clearly distinguish the results of each. It is possible that exercise can have different effects on each type, although more research into this comparison is needed. To get a better idea of how exercise might affect various types of asthma differently, future studies
should implement the same exercise protocol for both groups and analyze differences in pulmonary function, FeNO, and exercise tolerance. In order to do such a comparison and with generalizability, a bigger sample is needed.

5.8 Conclusions

HIIT has shown to be a time-efficient and beneficial exercise method with little to no safety risk for asthmatics. Although the lung inflammation levels and pulmonary function measures of the asthmatics did not improve, at the same time they did not worsen. Moreover, practicing an exercise routine can make asthmatics more comfortable with the idea of exercise. At the very least, this thesis has shown that HIIT and exercise in general is as beneficial for asthmatics as it is for healthy individuals without any major risks. Just as regular exercise is strongly recommended for all people for improvement of general well-being and reduction of all-cause mortality risks, this current study has shown that the same can be said for the asthmatic population and even the subpopulation of asthmatics with EIB. The findings that this HIIT protocol was safe and improved feelings of comfort with exercise in general among the asthmatic group is important because of the major obstacles facing asthmatics in regards to an active lifestyle: anxiety about exacerbating their condition and daily time constraints. More importantly, removing these exercise barriers with a safe and time-efficient routine such as HIIT can help prevent the asthmatic population from developing more serious conditions strongly associated with inactivity, such as obesity, diabetes, and heart disease.
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Appendix A

Comfort Level Questionnaire

*Name:* 

*Date:* 

**Comfort Level Questionnaire**

<table>
<thead>
<tr>
<th>Disagree</th>
<th>Strongly Agree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My body is relaxed right now</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>2. I want to exercise</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>3. I feel confident about exercising</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>4. I'm inspired to do my best</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>5. I'm afraid of exercising because of my condition</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>6. I do not feel healthy right now</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>7. I'm afraid of what is next</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>8. I do not like it here</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>9. I need to be better informed about my health</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>10. The nose clip and the mouth piece make me anxious</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>