The Acute Effects of High Intensity Interval Exercise on Pulmonary Function and Exhaled Nitric Oxide in Adults with Asthma

A Thesis Submitted to the College of Graduate Studies and Research in Partial Fulfillment of the Requirements for the Degree of Master of Science in the College of Kinesiology University of Saskatchewan, Saskatoon

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Abstract

Introduction: People with asthma suffer from lower fitness levels when compared to their peers. The abnormal respiratory response to exercise, known as exercise induced bronchoconstriction (EIB), in the majority of people with asthma is a barrier to improving fitness levels. EIB severity can be increased with airway inflammation, which can be measured by exhaled nitric oxide (eNO). One exercise protocol, high intensity interval exercise (HIIE), may decrease the risk of developing EIB in people with asthma. HIIE warm up studies have demonstrated that HIIE is feasible and reduces the incidence of EIB in subsequent exercise bouts. HIIE may be ideal for people with asthma because it can decrease the duration of high ventilation that can trigger EIB, and improve their fitness levels. The purpose of this study is to compare the acute respiratory effects of traditional constant workrate exercise to a novel HIIE protocol in adults with asthma.

Methods: 5 females and 2 males with asthma were recruited to perform two randomly assigned exercise protocols: HIIE (30 seconds of 140% the peak workrate and 90 seconds at 20%) and constant workrate exercise (CWR) (60% peak workrate). Workrates were determined by a peak cardiopulmonary exercise test. Measures of pulmonary function and airway inflammation were done pre and post exercise protocols. During exercise protocols, operational lung volumes, heart rate, rating of perceived exertion (RPE) was obtained.

Results: FEV_1 decreased significantly in both exercise protocols (HIIE 3.91± 0.65 to 3.33 ± 0.61 vs. CWR 3.90 ±0.50 to 3.09 ± 0.63). eNO measurements decreased after both exercise protocols (HIIE 40.4± 34.8 vs. CWR 42.1 ± 36.3.

Conclusion: FEV_1 and eNO findings are similar in HIIE and CWR exercise in adults with asthma, therefore, the novel HIIE is a feasible exercise protocol to help improve fitness levels of adults with asthma.

Acknowledgements

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Dedication

I would like to dedicate my thesis to my family, friends, and husband. To my parents, Wanda & Ken, without your unconditional support, guidance, and love I would not have faith in myself to pursue my own educational road through university. To my younger siblings, Mollie, McKenna, and Merik, thank you for reminding me that family is always more important than getting any degree. To my many wonderful friends, thank you for your welcome distractions of coffee dates, dance parties, and letting me listen to how your lives are going to keep me happy. And, to my husband, thank you for finishing your masters first and for sharing my belief that exercise is an important part of living our long, healthy life together.

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Chapter 1

Scientific Framework

1.1 Context

People with asthma have lower fitness levels when compared to their peers[1]. Low cardiorespiratory fitness levels not only increase disease risk factors similar to those seen in the healthy population, but people with asthma suffer additionally with poor disease control, increased asthma symptoms, and a general decrease in quality of life [2-4].

The benefits of regular exercise are well known for people with asthma; however, exercise has the potential to trigger exercise-induced bronchoconstriction (EIB) in a high percentage of people with asthma[5,6]. EIB may be causing people with asthma to refrain from exercising for extended periods which puts people with asthma at a greater chance of becoming deconditioned[2,4,7-9]. EIB can be avoided while exercising when utilizing appropriate exercise modes. New exercise protocols need to be designed and evaluated for people with asthma to improve their fitness levels without provoking EIB.

High intensity interval exercise (HIIE) may be an appropriate mode of exercise that will not provoke EIB. HIIE decreases the risk of developing EIB by two key processes: 1) HIIE may utilize the refractory period, the period up to 3 hours after exercise where less bronchoconstriction occurs, with the use of intervals that may allow people with asthma to exercise for longer periods of time[10-12] and 2) Interval exercise with periods of high and low ventilation rates may lead to less chance of developing EIB. During constant work rate exercise, high ventilation causes the airway surfaces to cool and dry out and this is thought to lead to EIB[13,14]. Interval exercise may lead to less time spent in a high ventilation zone and less chance of water loss occurring in the airway surfaces.

1.2 Objective

The objective was to investigate the acute effects of HIIE on pulmonary function, markers of inflammation, and respiratory responses during exercise in adults with asthma. The primary outcome measure is forced expiratory volume in 1 second (FEV_1). The secondary outcome measures are eNO, airway resistance (R_{AW}), respiratory rate (RR), ventilation (VE), and inspiratory capacity (IC).

1.3 Literature Review

1.3.1 Asthma

There are approximately 300 million people worldwide and 2.3 million Canadians with asthma and the prevalence is increasing[15, 16]. Asthma is defined by the Global Initiative on Asthma (2008) as:

> " a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. . . These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment"

The pathogenesis of asthma is complex. There are interactions between host and environmental factors that influence the risk of asthma development and the type of triggers[15]. The host factors are primarily genetic and the environmental factors include: air pollution, exposure to tobacco smoke, and timing of infectious disease exposures during the first year of life[15].

The diagnosis of asthma can be established based on the description of episodic symptoms and a positive family history of asthma[15]. Further investigations can be done such as pulmonary function tests (PFTs), provocation challenge tests, and measures of airway inflammation[15]. PFTs can be done to confirm airflow limitation and demonstrate the degree of reversibility[15]. When no airflow limitation is present further investigations can include provocation challenge tests. Methacholine, mannitol, and exercise challenge tests are all types of provocation challenge tests and they measure the level of airway hyperresponsiveness[15]. Direct and indirect measures of airway inflammation can be measured with sputum cell counts for inflammatory cells and fraction of exhaled nitric oxide levels respectively[17].

Asthma disease severity is based on the level of symptoms, airflow limitation, and pulmonary function variability[15]. The four categories, in increasing severity, are: intermittent, mild persistent, moderate persistent, and severe persistent[15]. The level of severity can change due to seasonal variability, exposure to allergens, medication use, and cardiorespiratory fitness levels[18,19].

Episodes of reversible airway obstruction, i.e. bronchoconstriction, can be triggered by a variety of common environmental stimuli such as animal dander, pollen, and exercise[15,20]. Common treatment options for adults with asthma include controller medications and reliever medications[15]. The effectiveness of controller medications depends on compliance and studies have shown that patient compliance is low [21-23]. Reliever medications include rapid acting inhaled β2 agonists and anticholinergics[15]. Reliever medications are commonly prescribed to people with asthma with EIB and they are directed to use prior to exercise as a prophylactic.

Exercise is another effective treatment option and is gaining evidence in helping with disease control [2,5,24,25]. EIB is seen in the majority of people with asthma, who try to exercise,

and can pose challenges in convincing people with asthma that increasing their fitness level may be as beneficial as using their medications[11,18].

1.3.2 Benefits of Exercise in Disease Management

People with asthma often suffer from daily to seasonal variability of symptoms[18]. This symptom variability is based on a number of factors, including exposure to allergens, viral infections, and stress[18]. When pulmonary function is decreased, respiratory symptoms increase and individuals with asthma are less likely to be active. One study showed that when respiratory function, measured by $FEV_{1,}$ was lower at the start of their day, people with asthma had lower physical and social activity later in the day[19]. During times of increased respiratory symptoms, people with asthma are less likely to be active. When people with asthma go through repeated periods of inactivity, their cardiorespiratory fitness levels can decrease[19]. This decrease in fitness level can lead to further increases in asthma symptoms, poor disease control, and a general decrease in quality of life [2-4]. A vicious cycle of decreasing activity due to an increase in symptoms that leads to a decrease in activity, occurs similar to that seen in chronic obstructive pulmonary disease [26,27].

There are many benefits of regular exercise in healthy populations[28]. In healthy populations, there is evidence to suggest that 150 minutes a week of exercise can decrease the risk of developing cardiovascular disease, stroke, hypertension, colon cancer, breast cancer, type 2 diabetes, and osteoporosis[28]. Along with the above benefits, people with asthma can have disease specific benefits from being regularly active and would see their low cardiorespiratory fitness levels improve[2,8,9,29]. Additional disease specific benefits include, decreased asthma symptoms, chance of developing an asthma exacerbation, risk of developing EIB, airway inflammation, dyspnea, increased FEV_1, and improvements in quality of life[2,4,8,9,24,29]. These

benefits are crucial to improving disease control. Periods of inactivity caused by increases in asthma symptoms lead to increased risk of deconditioning. Deconditioning can lead to periods of increased asthma symptoms, increased body mass index (BMI), decreased quality of life , and ultimately, increased health care costs[1,2,10,18,30].

There are also acute benefits of exercise if EIB is not triggered. A bronchodilatory response to exercise is one of the most beneficial[7]. The bronchodilatory response will occur even if people with asthma have their lungs bronchoconstricted with methacholine prior to the onset of exercise[6]. Despite a strong initial bronchodilatory response, as exercise time and ventilation rates increase, pulmonary function begins to decrease and airway resistance increases. This decrease in pulmonary function can cause increased asthma symptoms and increase the likelihood of dynamic hyperinflation (DH) and increased respiratory muscle work as well[7]. DH is the temporary and variable increase in end expiratory lung volume (EELV) above its baseline value[31]. Significant DH can be produced with mild bronchoconstriction brought on by methacholine challenge testing or during exercise [32-34].

Research into the acute respiratory responses to different exercise protocols for people with asthma is needed. Understanding the acute respiratory responses is important in helping people with asthma. Determining how different exercise protocols affect people with asthma will help in overcoming the initial barrier of getting active. Regular exercise will lead to better asthma control and many other benefits previously stated[2,4,8,9,24,29] . The long term effects of regular exercise for individuals with asthma are promising; however, the acute effects of different exercise protocols still need to be evaluated in adults with asthma. Finding an exercise protocol that assists them to overcome the initial barriers, particularly EIB, of exercise is crucial.

1.3.3 Exercise Induced Bronchoconstriction

EIB is found in a large majority of people with asthma and in certain athletic populations[11]. A positive diagnosis of EIB is still often difficult since exercise testing can only be done in exercise physiology laboratories[11]. EIB can be diagnosed by spirometry when FEV_1 falls 10% or more post exercise[11]. EIB can occur in athletes without a diagnosis of asthma, even though they experience AHR and increased inflammation similar to people with asthma[35,36]. Athletes who train and compete in cold and humid air, such as elite cross country skiers, have a higher prevalence of EIB than other athletic populations[36-38]. Factors predisposing certain athletic population are unclear but it has been speculated that high intensity exercise could induce or promote airway inflammation, either from hyperventilation or from increased airway exposure to inhaled allergens or pollutants[39]. Other factors potentially predisposing athletes to EIB could be the predominance of the parasympathetic nervous system over the sympathetic[40]. EIB can be found in both people with asthma and athletic populations but the theories to explain the cause of EIB in people with asthma have been studied more extensively.

The three major theories behind the pathogenesis of EIB are osmotic, thermal, microvascular. These different theories attempt to explain how normal processes that occur in the airways during exercise are leading to an abnormal response of bronchoconstriction. The predominant theory is the osmotic theory. The thermal and microvascular theories may also play important roles in the development of EIB. All three theories are based on the fact that the cause of EIB is not exercise itself, but the increase in ventilation seen as a result of exercise and will be discussed in detail below[13,14]. The evidence for ventilation being the key cause of EIB, is demonstrated with eucapnic voluntary hypernea (EVH) of dry air[13]. EVH occurs when a subject voluntarily hyperventilates and causes bronchoconstriction[13]. Exercise may not be the crucial determinant of

the severity of EIB. The severity of airway inflammation, the rate of ventilation reached during exercise, and the water content of the inspired air are the crucial determinants[14].

The severity of EIB is thought to be related to airway inflammation caused by eosionophils through eosinophilic airway inflammation[41]. This type of inflammation can be measured by the eNO level present in the airways. These levels can be non-invasively measured with the use of chemiluminescence gas analyzers. eNO levels can be measured on a clinical basis to monitor airway inflammation but can also be measured acutely for research purposes. People with asthma who are experiencing high eNO levels should be aware of its relation to EIB severity, i.e. periods of increased airway inflammation can lead to a greater risk of developing EIB. The coupled risk of developing EIB and potentially increasing airway inflammation after exercise may lead to an increase in asthma symptoms and a decrease in activity levels of people with asthma[10]. Regular exercise has shown the ability to reduce airway inflammation overtime[4]. The acute levels of eNO measured after exercise to monitor the inflammatory response has been inconsistent in studies with participants with asthma and further study is needed [42-44].

The rate of ventilation and the water content of the inspired air that is reaching the lower airways are determined by several factors. Inspired air is usually fully conditioned once it passes over the nasal mucosa and enters the airways[13]. The lower airways ability to condition inspired air is dependent on ventilation rate, water content and temperature of the inspired air, temperature of the airway wall, and the availability of airway surface liquid to provide adequate humidification[45]. During exercise, breathing patterns change from nose breathing to mouth breathing once ventilation increases past 30 $L \cdot min^{-1}$ [46]. Water loss and cooling of the airways occurs during exercise when high ventilation rates are reached.

The likelihood of EIB increases with greater ventilation and with dryer, colder inspired air[47,48]. There is evidence that interventions that lead to a reduction in airway water loss, such as decreasing intensity and duration of exercise, increase the water content of inspired air, and breathing through the nose can lead to a decreased severity of EIB[49-51]. A reduction in airway water loss may be possible with HIIE since high rates of ventilation are kept short which may not lead to the airway surfaces drying.

Discovering the acute respiratory effects of different exercises protocols on respiratory measures is critical to helping people with asthma improve their fitness levels. It is important to identify which exercise protocols lead to less respiratory symptoms, including EIB, to help people with asthma engage in more regular physical activity. The benefits of regular aerobic training in people with asthma can decrease the severity of EIB. In people with asthma who have higher fitness levels there is a less abrupt increase in ventilation during exercise[24]. The greater the ventilation rate and the greater number of airway generations required to condition inspired air, the greater the likelihood of EIB. A greater number of airway surfaces involved during ventilation increases the risk of triggering EIB This fact is particularly important when considering the osmotic theory.

1.3.3.1 Osmotic Theory

The *osmotic theory* proposes EIB is caused by increased osmolarity of the airway surfaces[13]. Increased osmolarity of the airway surfaces leads to water loss in the airways and the release of local mediators, such as histamine[13]. The water loss occurring with high ventilation leads to an increase in osmolarity of the airway surface. The increase in osmolarity is postulated to lead to the degranulation of airway mast cells. Once degranulation occurs, the inflammatory cascade continues with the release of mediators, such as, prostaglandins, leukotrienes, and

histamine leading to bronchoconstriction. Along with mast cell degranulation, other inflammatory processes can be activated including lymphocytes, eosinophils, epithelial cells, neutrophils[13,14] . Evidence supporting this theory includes the role of leukotrine blockers, the location of mast cells, and degranulation of these mast cells. Leukotrienes play a potential role in the development of EIB since interventions that use leukotriene blockers are effective in reducing EIB [11].

People with asthma have an increased number of mast cells and higher density of mast cells and mucous glands in the airway smooth muscle[52]. The increased presence of mast cells and mucous glands suggest their involvement in bronchoconstriction[52]. The degranulation of mast cells, leading to the release of histamine, is difficult to measure because of histamine's short half life. Histamine can be indirectly measured with markers such as, 9α,11β-prostagladin (PG) F_2 . PG F_2 has been shown to increase with EIB[53]. Other studies have shown that even with a greater mast cell density, when people with asthma exercised there was not a cellular influx of histamine into the airways[54,55]. Mast cells may be causing the change in osmolality in the airways which may be triggering the release of other inflammatory mediator pathways leading to EIB[54,55] .

1.3.3.2 Thermal Theory

The *thermal theory* is based on the normal cycle of cooling and rewarming of the airways during and after exercise[13]. During exercise, when ventilation rates increase, the airways will progressively cool because there is not adequate time to humidify and warm inspired air[56]. This progressive cooling of the airways occurs in both healthy adults and people with asthma[56]. Once exercise has ceased and ventilation returns to normal the airways rapidly rewarm[14]. Reactive hyperemia occurs in the bronchial microvasculature and edema of the airway wall[14].

In people with asthma who experience EIB, this rewarming process happens much more rapidly and remains elevated for a longer duration when compared to healthy adults[56,57]. These two findings suggest people with asthma have a different microvascular response when experiencing EIB. The difference in microvascular response is the basis of the *thermal theory*. Evidence from studies has shown warming of the airway after inhalation of cold, dry air can cause EIB[13,48,56]. The *thermal theory* proposes that the release of local inflammatory mediators is not the cause of EIB. The conflicting evidence for the *osmotic therory* that the degranulation of mast cells does occur and is the cause of EIB, suggests the *thermal theory* may only play a limited role in the pathogenesis and development of EIB[52,54,55].

1.3.3.3 Microvascular Theory

The *microvascular theory* attributes airway microcirculation as the cause of EIB[58]. This theory is linked to the remodeling process that occurs over time in people with asthma and the changes in bronchial circulation that occur during exercise. The bronchial capillary bed of most individuals with asthma is hypertrophied and hyperplastic[58]. The difference in the bronchial capillary bed in asthma is due to airway remodeling and the increased production of several growth factors that occurs over time. These growth factors lead to an increased number of new blood vessels, airway epithelial cells, and an increased secretion of vascular endothelial growth factor (VEGF)[59,60] .

VEGF has been linked to the development of EIB[61]. VEGF stimulates endothelial cell proliferation and increases microvascular permeability. Significant correlations have been found between airway microvascular permeability and the severity of EIB[61]. These findings suggest an increase in microvascular permeability induces airway wall edema and follows the development of EIB. This increase in microvascular permeability is a likely cause of EIB since bronchial

circulation within the lungs can influence airway geometry and lead to vascular engorgement, capillary leakage and edema formation that can lead to bronchoconstriction[58].

The exact mechanisms of EIB are still unknown. The current theories can still offer insight into creating new exercise protocols that may help in keep the risk of developing EIB for people with asthma. The *osmotic theory* suggests the airway surfaces are drying out with higher ventilation rates and the change of osmolarity is leading to the degranulation of mast cells[13,14]. Perhaps the drying of airways and the rest of the process would be less likely to occur if periods of high ventilation were shorter. A shorter period of high ventilation could be achieved with interval training, where short periods of high intensity, high ventilation, are combined with low intensity, lower ventilation. These periods of lower ventilation may give adequate time for ventilation and the risk of airway drying to decrease. The *thermal theory* proposes that when ventilation rates increase, the airways cool because there is not adequate time to humidify and warm inspired air[56]. This proposed mechanism of triggering EIB can be solved if participants breathe warm humidified air; however, this type of environment is not always available[56]. A more realistic approach would be to develop an exercise protocol that allows more time to adequately warm inspired air. During HIIE, the lower intensity interval may give adequate time to do so. The *microvascular theory* is linked to the remodeling of the pulmonary vasculature that occurs over time in people with asthma and the changes in bronchial circulation that occur during exercise. This theory seems the least likely to be changed with the mode of exercise since changes to the airways are happening chronically versus the acute nature of the Osmotic and Thermal Theory. Further investigations into the acute effects of HIIE are needed to shed light on these theories and identify potential mechanisms.

1.3.4 Adverse Effects of EIB on Exercise Response

People with asthma experience abnormal exercise responses. These abnormal responses include EIB, as described previously, and DH. EIB is thought to be caused by the increase in ventilation brought on by exercise and is not necessarily caused by exercise itself[1,15]. EIB is a well-documented potential side effect of exercise for individuals with asthma. Dyspnea and DH are other abnormal respiratory responses that may be occurring in people with asthma during exercise.

Dyspnea, or shortness of breath, is the primary symptom limiting exercise in people with chronic obstructive pulmonary disease (COPD) and in some people with asthma[62]. Those who stop due to dyspnea have greater DH and ventilatory constraints[62]. Dyspnea is thought to be caused by neuromechanical uncoupling of the respiratory system and dynamic lung hyperinflation[62]. In healthy individuals, ventilation rate (V_E) changes in accordance with neural central drive[62]. Even though V_E increases during exercise, medullary output remains appropriate and generally there is no feeling of inspiratory difficulty[62]. In people with COPD, and possibly in people with asthma, DH during exercise constrains tidal volume (VT) expansion and results in maximal shortening of the inspiratory muscles[62]. Once VT reaches the inspiratory reserve volume (IRV) ceiling, further increases in neural output to the respiratory system do not lead to increased mechanical output[62]. This neuromechanical uncoupling may form the basis for the perception of respiratory discomfort, which triggers respiratory distress[62]. Dyspnea during exercise is associated with progressive mechanical constraints regardless of the presence of DH in people with COPD[34].

DH has been found in patients with COPD and asthma[31,33]. DH can be measured through changes in inspiratory capacity (IC) [31,33]. DH is strongly associated with the dyspnea, and can be produced with provocation or exercise challenges in people with asthma[63-65]. DH is thought to be

caused by the development of expiratory flow limitation or the intensity of dyspnea[33,34,66-68]. During exercise, breathing frequency and ventilation increase, preventing adequate lung emptying during expiration before the next inspiration occurs[33]. DH causes a progressive shift in lung volumes towards total lung capacity (TLC) [33,66-68]. This progressive shift of lung volumes towards TLC occurs as the lungs become more hyperinflated, and the work of breathing increases as the efficiency of the inspiratory muscles to generate force decreases[66-68]. In a study by Kosmas et al. (2004), DH occurred in the majority of participants with asthma even if normal spirometry results and no EIB were present[69]. Dyspnea and DH may both be playing an important role in the respiratory symptoms experienced during exercise in people with asthma even if EIB is not present. If the risk of EIB can be kept low with HIIE it may keep dyspnea and the chance of developing DH low as well.

1.3.5 Asthma and High Intensity Interval Exercise

HIIE could be ideal for people with asthma to achieve maximal health benefits. HIIE has the potential to improve cardiorespiratory fitness levels while keeping the risk of EIB development low[7,8]. HIIE training studies have shown that a HIIE swim and land base training programs lasting ten weeks reduced the risk of EIB development[8,29]. HIIE training also provided a safe and effective exercise treatment option for adults with asthma[8,29]. During swim training, participants experienced acute bronchodilatory response that lasted one hour post exercise[8]. After the ten weeks of training, exercise capacity was increased and asthma symptoms, including EIB were reduced[8]. Land based HIIE training has been shown to be as beneficial as swim based high intensity interval training[29]. The majority of participants (68%) in the swim study continued to be physically active and maintained cardiovascular and lung function when follow up was conducted three years later[70].

HIIE training studies have been successful in showing adults with asthma are able to participate in high intensity interval exercise, and as result, maintain an active lifetstyle[8,29]. These training studies did not include all of the acute respiratory effects or suggest a potential mechanism for the benefits of HIIE for adults with asthma. Further investigations are needed to examine the acute respiratory effects of HIIE. HIIE warm up exercises have shown the acute respiratory effects and potential benefits due to utilization of the refractory period (RF) [10,12]. The RF is the time after the initial bout of exercise during which further exercise will evoke less or no EIB[10,12]. In a study by Mickleborough et al (2007) the development of EIB was reduced with the use of a HIIE warm up at an intensity of 85-90% maximum heart rate[12]. It appears EIB can be blunted in a second bout of exercise if it is done less than 4 hours after the first bout of exercise[71]. The potential mechanism for not developing EIB was the utilization of the refractory period, which is seen in approximately 50% of people with asthma. This mechanism may combat the degranulation of mast cells that are thought to occur in the *osmotic theory*[12,72]. It is not known if HIIE warm up RF findings hold true for an HIIE protocol. Further, it is also unknown if higher intensity, above 90% predicted maximal heart rate, interval exercise in adults with asthma is tolerable and will utilize the refractory period.

1.4 Hypotheses

I hypothesize 1) that the primary outcome measure, FEV_1, will be decreased in both constant work rate (CWR) and HIIE exercise protocols and will decrease greater in CWR when compared to HIIE 2) markers of inflammation, eNO and R_{AW}, will decrease and increase, respectively, in both CWR and HIIE exercise protocols. eNO will decrease greater and R_{AW} will increase greater in CWR when compared to HIIE 3) Respiratory responses during exercise, IC, RR & V_E, will be increased in both CWR and HIIE exercise protocols and IC will increase

greater in CWR when compared to HIIE, whereas, RR and V_E will increase greater in HIIE when compared to CWR and 4) Markers of inflammation and respiratory responses during exercise will be associated to the change in FEV_1.

Chapter 2

Methods

2.1 Participants

Twelve, male and female adults over the age of 18 years of age with asthma diagnosed by a physician were screened by asking inclusion criteria questions and performing baseline testing during day one and two for this study. Seven participants met the inclusion criteria which included: a current diagnosis of asthma; tidal breathing methacholine provocation concentration to cause a 20% decrease in FEV_1 (PC_{20}) ≤ 16 mg/ml; FEV_1 > 65% predicted, and no respiratory tract infection or allergen exposure for ≥ 4 weeks. Written informed consent was collected from all participants prior to data collection and the study was approved by the University of Saskatchewan Biomedical Research Ethics Board. (See Appendix A for a copy of the Ethics: Certificate of Approval). All testing was done at Royal University Hospital in Saskatoon Saskatchewan.

2.2 Experimental Design

The research study was conducted using a randomized crossover design and used a within subject repeated measures design to assess two different exercise protocols (high intensity interval and constant work rate) over time. Participants were screened for inclusion criteria during day one and two of the study. All of the baseline tests were done according to American Thoracic Society (ATS) guidelines[73-78]. All study visits were separated by a minimum of 24 hours and were completed in two weeks to limit potential environmental exposure such as changes in air quality and seasonal variability. Day 1 included eNO measurements, spirometry, and a methacholine challenge test. On Day 2, all participants performed full PFTs followed by a

maximal cardiopulmonary exercise test. Randomization of participants occurred on day 3. On day 3 and 4, the participants performed pre and post exercise eNO, R_{AW} and TLC measurements, followed by one of the two exercise protocols. During exercise, FEV_1 and IC measurements were performed. FEV_1 measurements were performed again at 0, 5, 10, 15, 20, 30 minutes post exercise protocols. The study design and measures for each testing day are illustrated below in Figures 2.2.1 and 2.2.2.

Figure 2.2.1 Baseline & Screening Days – Day 1 & 2

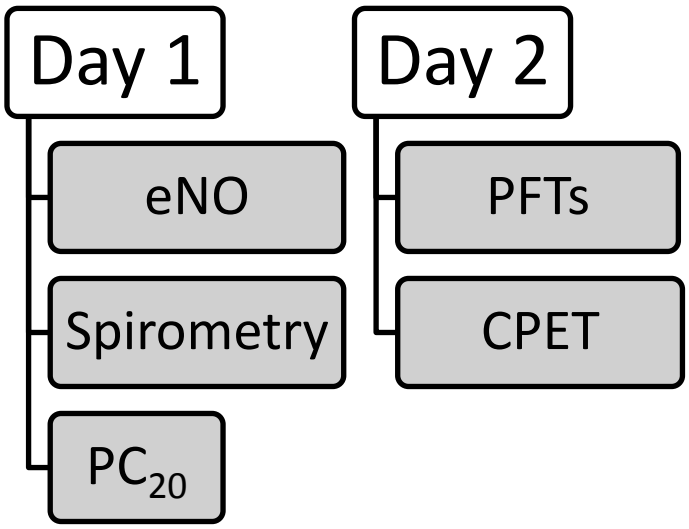
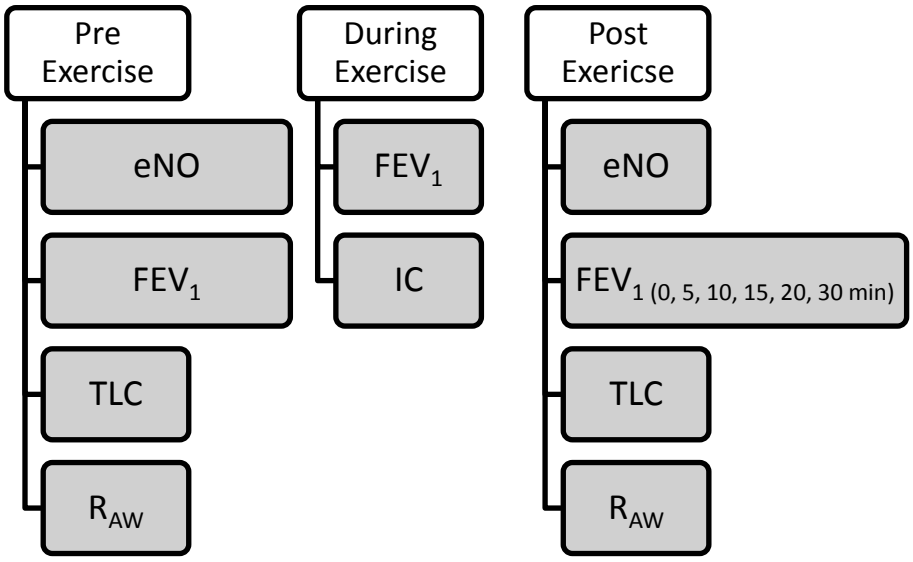


Figure 2.2.2 Exercise Days – Day 3 & 4



2.3 Measures

2.3.1 Fraction of Exhaled Nitric Oxide (eNO)

eNO levels were recorded to measure airway inflammation. Baseline eNO levels were measured on Day 1. eNO levels were measured on exercise days pre and post exercise. eNO levels were measured using a chemiluminescence gas analyzer (Niox, Aerocrine Inc., New York, NY). Participants performed an inhalation to TLC followed by an exhalation with a constant flow rate of 50 ml/sec via a mouthpiece[79]. The procedure was performed in triplicate and recorded in parts per billion (ppb). The validity and reliability of this measurement device is high (r =0.98, p <0.0001)[80,81].

2.3.2 Methacholine Challenge Test (MCT)

The MCT was used to determine airway hyperresponsiveness. Baseline MCT PC_{20} was measured on Day 1. The MCT was performed using the standard 2 minute tidal breathing challenge as outlined in the current ATS guidelines[75]. The tidal breathing method was performed

using a Bennett Twin jet nebulizer (Puritan Bennett Corporation, Carlsbad, CA) calibrated to deliver an output of 0.13 mg/ml of methacholine. Participants wore noseclips and the aerosols were directed to the mouth over a period of 2 minutes via a loose-fitting facemask. Complete baseline spirometry was initially performed in triplicate and truncated FEV_1 maneuvers were performed at 30 and 90 seconds after the completion of each 2 minute inhalation period. The next cycle started 5 minutes after the start of the previous cycle. Sterile isotonic saline was first to be inhaled followed by doubling doses of methacholine. Concentrations from 0.03 mg/mL to 64 mg/mL were available. Change in FEV_1 was calculated from the lowest post-saline FEV_1 and lowest post-methacholine FEV_1. The challenge continued until FEV_1 fell $\geq 17\%$. PC_{20} was then interpolated or extrapolated from the log dose vs. dose response curve algebraically.

2.3.3 Pulmonary Function Tests (PFTs)

PFTs performed included: spirometry: lung volumes and capacities: and carbon monoxide diffusion capacity (DL_{CO}) tests assessed according to ATS standards[75-77]. The best of three trials for each measure was recorded.

FEV_1 was measured on day 2 for baseline and pre, during, and post exercise on day 3 and 4. FVC was measured on day 2 for baseline. TLC was measured on day 2 for baseline and pre and post exercise on day 3 and 4. R_{AW} was measured on day 2 for baseline and pre and post exercise on day 3 and 4. DL_{CO} was measured on day 2 for baseline. IC was measured on day 3 and 4 at rest and during exercise. PFTs (FEV_1, TLC, R_{AW}, DL_{CO}) were monitored pre and post exercise protocols using the Sensormedics, Vmax, which has been shown to be a valid measure[81]. Lung volume measurements (FEV_1 and IC) captured during exercise were measured using the Parvomedics system and also has been shown to be valid and reliable[82].

2.3.4 Maximal Cardiopulmonary Exercise Test (CPET)

An incremental exercise test was used to determine cardiorespiratory fitness levels and establish participant work rates during exercise protocols. The CPET was performed on Day 2. The CPET was performed to the standards of the ATS/ACCP[73]. The test began with a three minute warm up of unloaded cycling, followed by ramped increases in work rate until exercise tolerance. The work rate increment was individually determined based on their current exercise habits whereby individuals who were more active increased at a higher increment. Heart rate and ECG were monitored and recorded using a modified 3 lead ECG. Symptoms of dyspnea and leg fatigue were individually recorded using the modified Borg scale[83].

2.4 Exercise Protocols

Both exercise protocol, HIIE and CWR, days started with pre exercise measurements of eNO and PFTs. Participants then changed into comfortable workout clothes and were fitted with a heart rate monitor and fitted to the ergometer. Once seated, the participants were fitted with a head piece that would hold the mouth piece. Before the mouthpiece and nose clips were applied, the protocol was reviewed for stopping exercise. When the participant was ready, the mouth piece and nose clips were applied and then two minutes of resting data was collected while the participant rested on the bike. Five minutes of warm up at 50 Watts began after that time. The participant was counted down in the last 10 seconds before exercise began. Exercise lasted 20 minutes or to exercise tolerance and concluded with a cool down. During exercise, participants' ratings of perceived exertion (RPE) for shortness of breath and leg fatigue were individually recorded, flow volume loops, and heart rate were recorded at different intervals depending on the exercise protocol. When the participant reached exercise tolerance or completed 20 minutes of exercise the exercise was stopped and were instructed to cool down. Once the headpiece was

removed and the participant had cooled down, they performed post exercise measures for eNO and PFTs at 0, 5, 10, 15, 20, 30 minutes post exercise.

2.4.1 HIIE

The HIIE consisted of 30 seconds of high intensity exercise at 140% of their peak work rate and 90 seconds of low intensity exercise at 60% of peak work rate. Data was collected at the end of the each high intensity exercise bout.

2.4.2 CWR

Two minutes of resting data was collected while the participant sat on the bike. The participant then began their five minute warm up at 50 Watts. The CWR exercise consisted of the participants performing at 60 % of their peak work rate as determined by the CPET. Data was collected every two minutes.

The exercise intensities for the protocols were based on the participant's peak work rate established during their maximal CPET done on day 2. Therefore, participants would perform equal amounts of work if they were able to complete 20 minutes of exercise in both protocols.

2.5 Statistical Analysis

Using Statistica, a 2 x 2 repeated measures ANOVA was conducted with protocol (high intensity interval and constant work rate exercise) and time (pre vs. post or/peak) as factors to determine the differences within conditions for the primary outcome measure, FEV_1 and respiratory responses during exercise, RR, V_E and IC. The post exercise values were the lowest values within each data set and included FEV_1 and IC. The peak exercise values were the highest values within each data set and included RR and V_E. Tukey's post hoc analysis was used to determine condition differences in the presence of significant main effects. Pearson's r correlation coefficient was used to determine if significant relationships were evident between

the change in the primary outcome measure, FEV_1, to the change in makers of inflammation, eNO and R_{AW}, peak respiratory responses during exercise, V_E and RR, and the change in IC during exercise

Using SPSS, a 2 x 2 repeated measures ANOVA was conducted with protocol (high intensity interval and constant work rate exercise) and time (pre vs. post) as factors to determine the differences within conditions for markers of inflammation, eNO and R_{AW}, and TLC.

Using Excel, paired t-tests were conducted to assess significance between exercise protocols for total exercise time and ratings of perceived exertion. Alpha was set at 0.05 for all analyses. Data are presented as means and standard deviations.

Chapter 3

Results

3.1 Participant Demographics

Seven adults with mild to moderate asthma were included in this study and the participant demographics are presented in mean (±SD) for sex, age, BMI, VO_2 peak in Table 3.1.1.

Participants had a current diagnosis of asthma, (PC_{20})≤ 16 mg/ml, FEV_1 > 65% and no respiratory tract infection or allergen exposure for 4 weeks. Participant pulmonary function demographics are presented as mean (±SD) for airway inflammation, pulmonary function, airway hypersentivity, total lung volume, and diffusion capacity and can be found in Table 3.1.2. Medication use and withholding of medications prior to tests were done according to ATS guidelines[21].

The participant's exercise protocol watts, time, and rates of perceived exertion for end of exercise shortness of breath and leg fatigue are presented in Table 3.1.3. Participants exercised longer in the CWR protocol, $p < 0.05$. Rating of perceived exertion for shortness of breath and leg fatigue did not differ significantly between exercise protocols, $p > 0.05$.

Table 3.1.1 Participant Demographics

Characteristic	Pooled Data	Female	Male
Sex	2M:5F		
Age	23.0 ± 3.6	24.4 ± 3.1	19.5 ± 2.1
BMI	23.6 ± 2.0	24.2 ± 1.9	22.0 ± 1.3
VO_2 Peak (ml/kg/min)	40.4 ± 14.5	33.8 ± 8.4	56.8 ± 14.8

Mean ± Standard deviation, Body Mass Index (BMI), Male (M), Female (F)

Table 3.1.2 Participant Pulmonary Function

Characteristic	Data
FEV_1 (L)	3.97 ± 0.53
FEV_1 % predicted	106.0 ± 8.8
eNO (ppb)	47.7 ± 43.7
FVC (L)	4.81 ± 0.69
FVC % Predicted	112.0 ± 7.9
TLC (L)	5.95 ± 0.95
TLC % Predicted	107.0 ± 10.8
DL_{CO} (mmole $CO \cdot min^{-1} \cdot kPa^{-1}$)	28.9 ± 7.0
PC_{20} (mg/ml)	3.6 ± 3.5

Mean ± Standard deviation, Forced Expiratory Volume in 1 second (FEV_1), exhaled nitric oxide (eNO), Forced Vital Capacity (FVC), Total Lung Capacity (TLC), Diffusion Capacity (DL_{CO}), methacholine provocation concentration to cause a 20% decrease in FEV_1 (PC_{20})

Table 3.1.3 Participant exercise protocol summary

	HIIE	CWR
High Interval (watts)	308.0 ± 111.6	
Low Interval (watts)	44.0 ± 15.9	
Constant (watts)		132.0 ± 47.8
Time (sec)	886.5 ± 255.2	1119.8 ± 153.4*
RPE End SOB	6.4 ± 2.1	6.4 ± 3.0
RPE End Leg Fatigue	8.4 ± 1.7	6.9 ± 2.1

Mean ± Standard deviation, Shortness of breath (SOB), Rating of Perceived Exertion(RPE) * denotes significance at $p < 0.05$

3.2 Respiratory Responses during Exercise

3.2.1 Forced Expiratory Volume in 1 second (FEV_1)

There was a significant main effect of time on FEV_1 during exercise F (1,18) = 10.611, p = 0.00, power = 0.99, η^2 =0.64; Figure 3.2.1.1. One subject had a clinical definition of EIB, FEV_1 decrease greater than 10%, in HIIE exercise protocol. Missing data points occurred during exercise for both exercise protocols.

3.2.2 Respiratory Rate (RR)

There was a significant main effect of time on RR during exercise, F (1,18) = 32.296, p = 0.00, power = 1.00, η^2 =0.84; Figure 3.2.2.1.

3.2.3 Ventilation (V_E)

There was a significant main effect of time on V_E during exercise, F (1,18) = 34.992, p =0.00, power = 1.00, η^2 =0.85; Figure 3.2.3.1. Peak V_E reached during the CPET did not differ significantly with peak V_E achieved during the CWR and HIIE exercise protocols (99.7 ± 30.7, 86.9 ± 37.1, 99.4 ± 35.3, respectively, p >0.05).

3.2.4 Inspiratory Capacity (IC)

There was no significant main effect of time on IC during exercise F (1,15) = 0.882, p = 0.05, power = 0.19, η^2 =0.14; Figure 3.2.4.1.

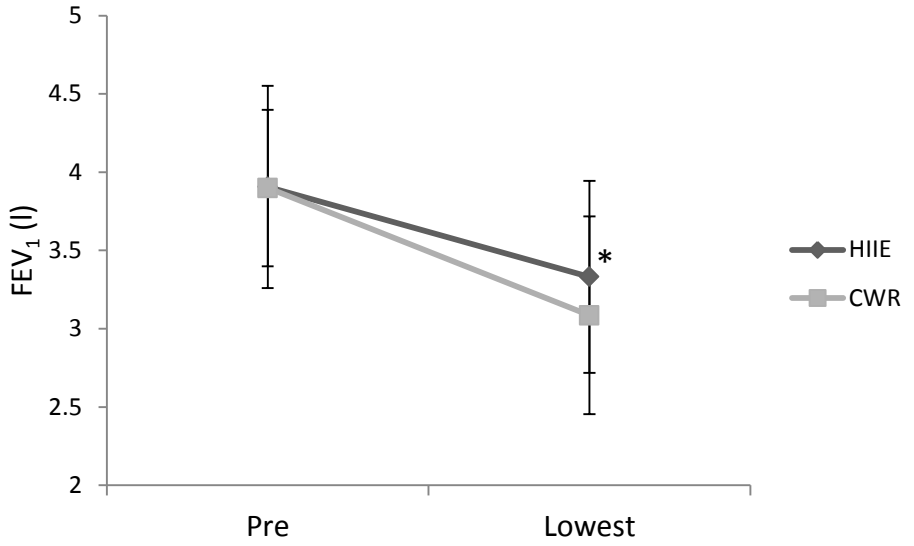


Figure 3.2.1.1 – Change in FEV_1 for both exercise protocols. Mean values are plotted. Values are in litres. FEV_1 decreased significantly in both exercise protocols over time, $p < 0.05$ High Intensity Interval Exercise (HIIE) and Constant Work Rate (CWR). * denotes $p < 0.05$

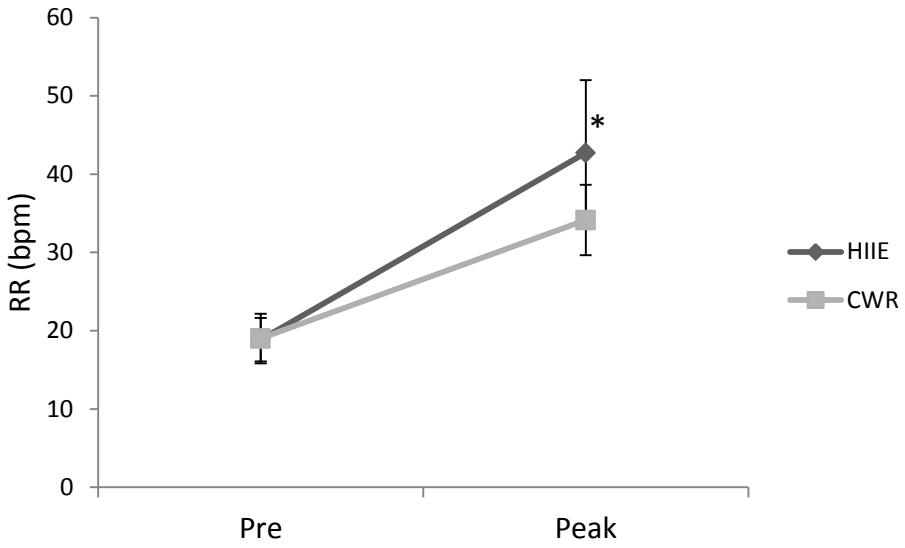


Figure 3.2.2.1 – Change in RR for both exercise protocols. Mean values are plotted. Values are in breathes per minute. RR increased significantly over time in both exercise protocols, High Intensity Interval Exercise (HIIE) and Constant Work Rate (CWR). * denotes p <0.05

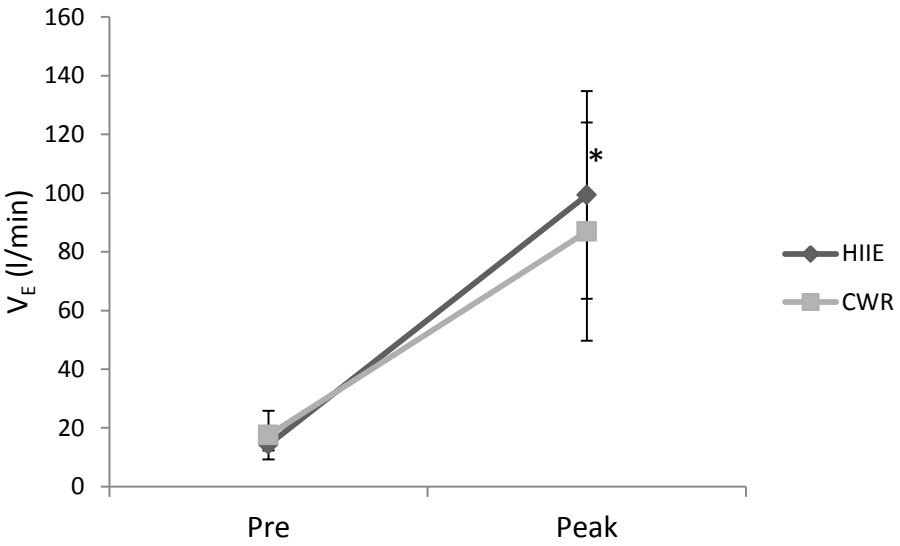


Figure 3.2.3.1 – Change in V_E for both exercise protocols. Mean values are plotted. Values are in liters per minute. V_E increased significantly in both exercise protocols over time. High Intensity Interval Exercise (HIIE) and Constant Work Rate (CWR). * denotes p <0.05

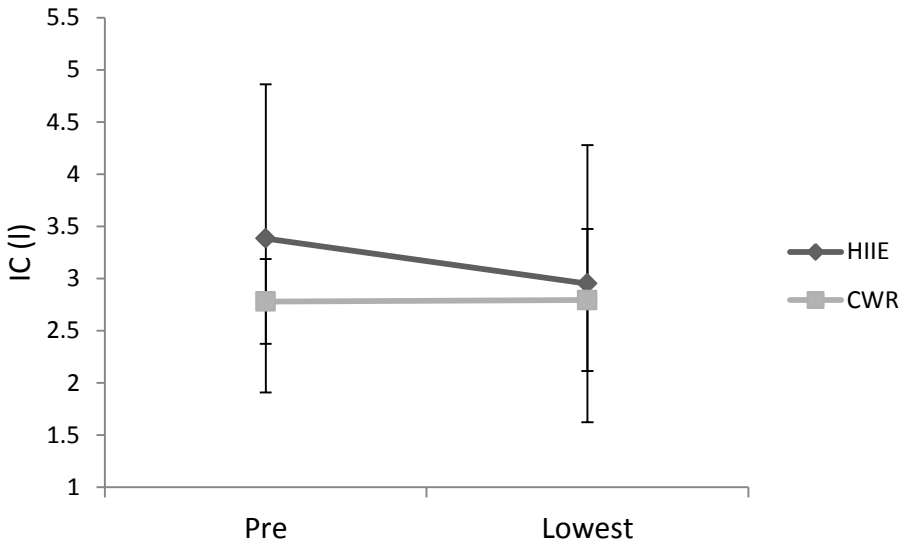


Figure 3.2.4.1 – Change in IC for both exercise protocols. Mean values are plotted. Values are in liters. IC did not change significantly in either exercise protocols over time. High Intensity Interval Exercise (HIIE) and Constant Work Rate (CWR). * denotes p <0.05

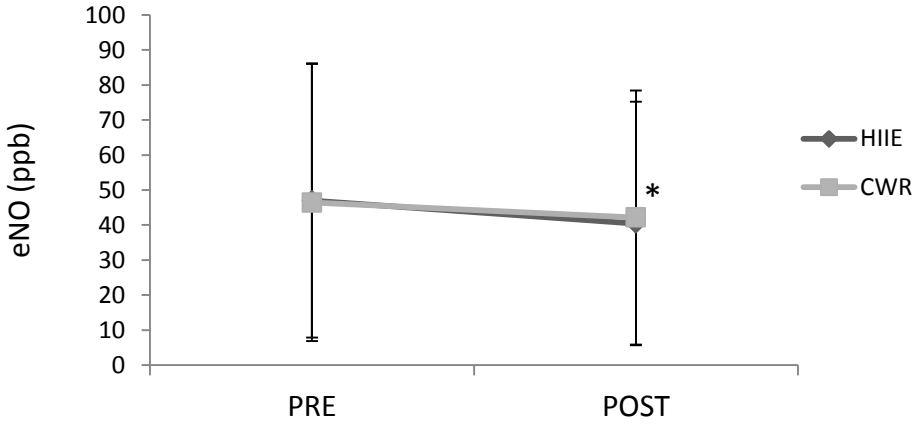
3.3 Markers of Airway Inflammation Pre and Post Exercise

3.3.1 Exhaled Nitric Oxide (eNO)

There was no significant interaction found between exercise protocols and time on eNO levels, F (1,12) = 0.659, p = 0.43 and no significant main effect of exercise type on eNO levels F (1,12) = 0.01, p = 0.98. There was a significant main effect of time on eNO levels found, F (1,12) = 14.861, p = 0.02; Figure 3.3.1.1.

3.3.2 Airway Resistance (R_{AW})

There was no significant interaction between exercise protocol and time on R_{AW}, F (1,12) = 0.03, p = 0.87, no significant main effect of time on R_{AW}, F (1,12) = 0.927, p = 0.36, and no significant main effect of exercise type on R_{AW}, F (1,12) = 0.269, p = 0.61; Figure 3.3.2.1.



F**igure 3.3.1.1 - eNO levels vs. time for both exercise protocols**. Mean values are plotted. Values are in parts per billion. There was a significant main effect of time on eNO levels in both exercise protocols. High Intensity Interval Exercise (HIIE) and Constant Work Rate (CWR). * denotes $p < 0.05$

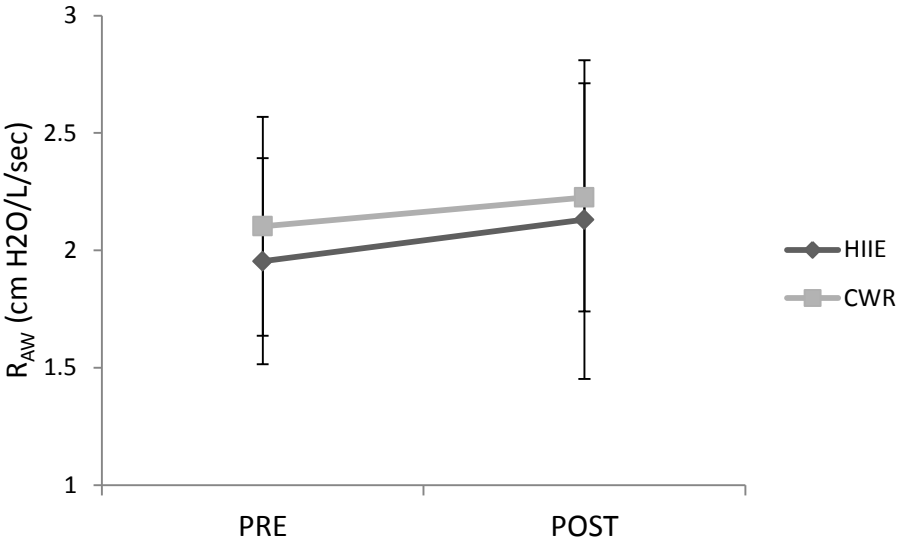


Figure 3.3.2.1 – R_{AW} vs. time for both exercise protocols. Mean values are plotted. Values are in centimeters of water ·liters^{-1}·second^{-1}. There were no significant differences found between exercise protocols and time. High Intensity Interval (HIIE) and Constant Work Rate (CWR). * denotes p <0.05

3.4 Operational Lung Volumes

3.4.1 Total Lung Capacity (TLC)

There was no significant interaction between exercise protocol and time on TLC, F (1,12) = .553, p =0.47, no significant main effect of time on TLC, F (1,12) = 553, p =0.47, and no significant main effect of exercise type on TLC , F (1,12) = 0.041, p = 0.84; Figure 3.4.1.1.

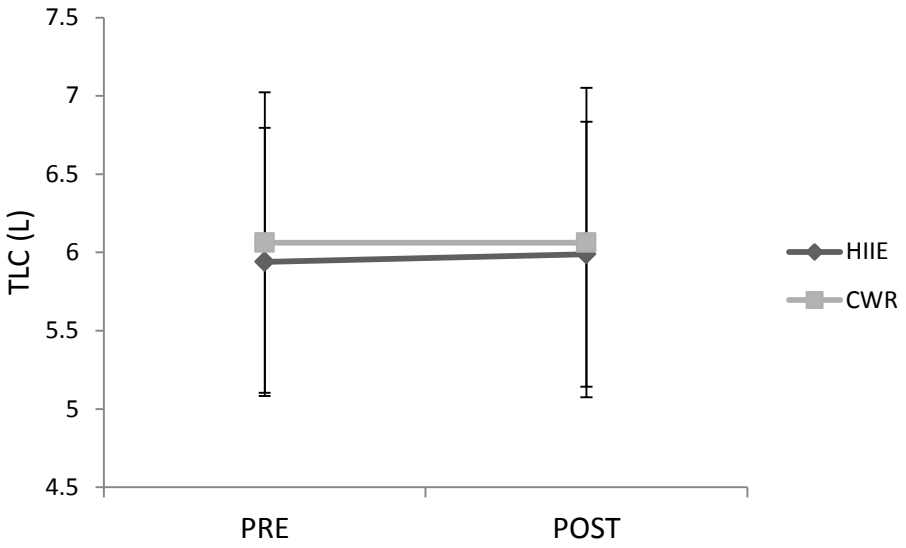


Figure 3.4.1.1 – TLC vs. time for both exercise protocols. Mean values are plotted. Values are in liters. TLC did not change significantly in either exercise protocols over time, High Intensity Interval Exercise (HIIE) and Constant Work Rate (CWR). * denotes p <0.05

3.5 Correlations

3.5.1 Markers of Airway Inflammation

Baseline eNO levels on both exercise days were significantly inversely related to post airway resistance, R_{AW} (HIIE r (6) = -0.86, p = 0.01 and CWR r (6) = - 0.75, p = 0.05).

On the HIIE and CWR exercise day, the change in FEV_1 was not significantly correlated with the change in eNO, r (6) = 0.70, p =0.08 and r (6) = -0.38, p = 0.39, respectively.

On the HIIE and CWR exercise day, the change in FEV_1 was not significantly correlated with the change in R_{AW}, r (6) = 0.09, p = 0.84 and r (6) = 0.18, p =0.71, respectively.

3.5.2 Respiratory Responses during Exercise

On the HIIE exercise day, the change in FEV_1 was not significantly correlated with peak RR and V_E, r (6) = 0.68, p = 0.09 and r (6) = 0.46, p =0.30 respectively.

On the CWR exercise day, the change in FEV_1 was not significantly correlated with peak RR and V_E, r (6) = -0.31, p = 0.50 and r (6) = -0.08, p = 0.87 respectively.

On the HIIE exercise day, the change in FEV_1 was significantly correlated with the change in IC, r (6) = 0.88, p = 0.01. On CWR exercise day, the change in FEV_1 was not significantly correlated with the change in IC, r(6) = 0.14 , p = 0.76.

Chapter 4

Discussion

4.1 Main Findings

This study has shown the acute respiratory effects of HIIE when compared to CWR in adults with asthma and partially supported our hypotheses. FEV_1 did decrease in both exercise protocols but did not decrease to a greater degree in the CWR when compared to HIIE; therefore, did not support the hypothesis that CWR would lead to an increased risk of EIB when compared to HIIE. The markers of inflammation, eNO and R_{AW}, decreased and remained the same, respectively, in both exercise protocols; therefore, did not support the hypothesis that eNO will decrease greater and R_{AW} will increase greater in the CWR when compared to the HIIE. Respiratory responses during exercise, IC, RR & V_E, remained the same for IC and increased for RR & V_E in both exercise protocols; therefore, did not support the hypothesis that IC would increase greater in CWR when compared to HIIE and that RR and V_E will increase greater in HIIE when compared to CWR. The change in FEV_1 during the HIIE exercise protocol was correlated with the change in IC; therefore, did not support the hypothesis that markers of inflammation and other respiratory responses (change in eNO, change in R_{AW}, peak RR and V_E) will be associated to the change in FEV_1.

All seven participants were able to perform the novel HIIE (140% peak work rate), with no adverse events, such as asthma exacerbations or the need to use rescue inhalers. This study has shown similar results to HIIE training studies in people with asthma, that were at a lower intensity, 80-90% maximum heart rate, where no adverse events occurred[8,29]. The finding of no adverse events is also similar to HIIE warm studies in people with asthma, which have also been done at a lower intensity, i.e. 85-90 % of maximum heart rate[12]. Concrete comparisons of this

novel HIIE is difficult since individualized peak work rates were used to determine exercise intensity in the present study, whereas prior studies have used maximum heart rate. Further research of varying HIIE intensities is needed to determine if there is an ideal HIIE intensity that does not cause a decrease in FEV_1 for people with asthma.

FEV_1 decreased in both exercise protocols but did not decrease to a greater degree in the CWR when compared to HIIE (Figure 3.2.1.1). These findings suggest that although EIB was detected, the findings were similar between the HIIE and CWR protocols. Individual results revealed that only one subject during the HIIE had a true clinical definition of EIB, a FEV_1 decrease greater than 10% post exercise. The findings of FEV_1 decreasing is not similar to HIIE warm up studies that have shown EIB was less likely to occur after doing a high intensity warm up[12]. This study has also not show similar results to HIIE training studies that have shown a bronchodilator effect up to one hour post exercise[8,29]. One possible acute mechanism to explain the EIB response could be no activation of the refractory period with interval exercise compared to repeated exercise bouts. Another possible factor could be the HIIE intensity was higher than the HIIE training and warm up studies and led to a decrease in FEV_1.

The markers of inflammation, eNO and R_{AW}, decreased and remained the same, respectively, in both exercise protocols (Figure 3.3.1.1 & Figure 3.3.2.1). This decrease in eNO is similar to those reported in other studies of adults with asthma[86,87]. Increased ventilation and pulmonary blood flow may cause the decrease in eNO post exercise[87]. The increased ventilation increases the amount of NO to be exhaled from the body, which after exercise causes eNO to decrease[87]. Pulmonary blood flow may have led to the decrease in eNO, but it was not measured in this study[87]. An increased pulmonary blood flow could have removed NO from the pulmonary circulation, causing eNO to decrease. Although eNO did decrease, it does not necessarily reflect

a decrease in inflammation but show the potential of an inflammatory process being involved. To study the effects of inflammation, blood samples, sputum induction, or 24 hour post eNO levels would have been required to measure acute inflammatory markers.

R_{AW} and TLC were not significantly different from pre to post exercise in either exercise protocol. In this study, airway inflammation, measured by eNO, decreased in both exercise (Figures 3.3.1.1). The decrease in eNO may explain why no significant changes were seen in R_{AW}. In studies of healthy males, R_{AW} was unchanged during exercise and TLC was unchanged post exercise[88,89]. In studies with people with asthma and people with COPD, dyspnea and the subsequent increase in EELV, and not TLC, appears to be the cause of DH and increases in airway resistance[72,90,91]. Our findings support these prior studies since TLC did not change significantly in either exercise protocol and the ICs measurements captured during exercise were valid.

Respiratory responses during exercise, IC, RR & V_E, remained the same for IC and increased for RR & V_E in both exercise protocols (Figure 3.2.2.1, Figure 3.2.3.1, & Figure 3.2.4.1). The lack of increase in ICs, and therefore no DH expected, could be due to the lack of change in R_{AW} in both exercise protocols[72,90,91]. However, the decrease in FEV_1 seen in both exercise protocols would be likely to produce DH in people with asthma and other clinical populations such as COPD[32-34]. This finding is unclear and perhaps with more subjects, the ICs would have increased as expected.

The increase in RR and V_E is to be expected due to the increasing metabolic demands of the body during exercise. V_E did not differ significantly between exercise protocols but since total V_E was not analyzed, making definite conclusions is difficult. V_E was captured in the HIIE at the end of the high intensity interval, when V_E would potential be the highest. V_E would likely

be lower if captured during the lower intensity interval or averaged across the entire time period. More specific research into how V_E is involved is needed to clarify the exact involve of V_E.

Baseline eNO levels were correlated with R_{AW} in the HIIE, but only approached significance for the CWR condition (p=0.051). Airway inflammation has been found to correlate with airway resistance because R_{AW} is affected by bronchoconstriction and inflammation of the airways[41]. Since significance was close for the CWR condition the finding is probably due to low participant numbers. The change in FEV_1 was not significantly correlated with the change in eNO, change in R_{AW}, peak RR or peak V_E. These findings are not similar to other studies that have shown relationships between severity of EIB and eNO[41]. As airway inflammation is increased, the severity and likelihood of causing EIB, and seeing a decrease of FEV_1 is expected. The relationship has also been seen in prior studies between change in FEV_1 and change in R_{AW}[6]. As FEV_1 decreases, and bronchoconstriction occurs, RAW would be expected to increase, however, our study did not show this relationship. The change in FEV_1 during the HIIE exercise protocol was correlated with the change in IC but not in the CWR exercise protocol. IC was expected to increase, and since it did not, the lack of correlation between the change in FEV_1 and the change in IC in the CWR could be explained by this finding.

Conclusions on the underlying physiological mechanisms involved in this study are difficult, but it may be speculated that changes in airway inflammation may have been involved and would support that the EIB seen in this study was caused by the *osmotic theory*. Since the marker for inflammation, eNO, was measured and it is an indirect measure of airway inflammation further studies are needed to show conclusive evidence that the EIB mechanisms were related to changes in airway surface osmolarity[13,14,56]. Further study would also be needed

to rule out that the progressive cooling and rewarming of the airways was not occurring during periods of high and low ventilation during the HIIE protocol.

4.1.1 High Intensity Interval Exercise

This study is beneficial for people with asthma because there were no adverse events associated with either exercise protocol in these participants. This novel HIIE protocol may provide people with asthma a type of exercise to try if they are having difficulty exercising due to fluctuating asthma symptoms and EIB being caused by CWR. While the long term benefits were not examined in this study, HIIE has many potential benefits, discussed below, and has been shown in previous studies as a safe way to improving cardiorespiratory fitness while keeping the risk of EIB development low in people with asthma[7,8,29]. Other benefits of HIIE in healthy participants include being enjoyable, greater lipid metabolism and similar physiological remodeling as seen in endurance training [92-94]. Sprint training, another form of HIIE, has been found to be enjoyable when compared to continuous exercise, despite the RPE being higher in the HIIE group[92]. When short bouts of anaerobic exercise are coupled with aerobic exercise, greater lipid metabolism occurs, which is important for reducing BMI in healthy people[93]. In healthy participants, HIIE training induced metabolic adaptations during exercise that are comparable to endurance training[94].

This study may also benefit people with other respiratory diseases, like COPD, who are suffering from similar challenges to improve fitness levels. In people with COPD, interval exercise is better tolerated, less breaks are required and better adherence occurs compared to continuous exercise[84,85]. The participants in our study were able to tolerate the HIIE protocol and were more likely limited by leg fatigue than dyspnea (Table 3.1.3). COPD, like asthma, is an obstructive lung disease and comparisons can be made between populations, however, since the

participants in this study were relatively young and healthy comparing them to athletes with EIB may be more appropriate.

Athletes with EIB may benefit from this novel HIIE since it is speculated that high intensity exercise can increase airway inflammation[39]. HIIE may give athletes with EIB the potential to decrease airway exposure to inhaled allergens or pollutants due to intermittent periods of lower ventilation, therefore, less potential to promote airway inflammation. HIIE will also be more beneficial to certain athletic populations with high rates of EIB, who train and compete in a fashion similar to HIIE, i.e. ice hockey, versus endurance athletes, i.e. cross country skiers[36,95]. Further research is needed to draw conclusions between people with asthma and athlete populations who suffer from EIB.

4.2 Limitations

The small number of participants in this study limits the ability to make concrete statistical conclusions, especially when attempting to review individual and gender differences in significant and non-significant findings. With a larger sample size more conclusive evidence for HIIE as an exercise option for people with asthma could be found. Adding participants who are known to exhibit EIB would be of benefit to clearly show if either exercise protocol decreased the risk of developing EIB. A healthy control group would be needed to draw any concrete conclusions that the findings in this study were only true to people with asthma. For some of the measures, during exercise data was missing, therefore, full exercise data could not be analyzed and interpreted.

4.3 Practical Implications and Future Research

This study provides evidence to support HIIE as another alternative for adults with asthma who are trying to increase fitness levels. HIIE may be what they need to succeed and

offer additional benefits when compared to CWR. Other respiratory disease populations, such as COPD, who also suffer from decreased fitness levels, may benefit from HIIE.

Future research should be focused on chronic training studies to determine the long term effects and benefits of HIIE on pulmonary function and airway inflammation in people with asthma. Future research should also investigate if people with asthma are able to continue to be active after the training studies are complete.

Chapter 5

Conclusions

The objective of this study was to compare the acute respiratory effects of traditional CWR exercise to a novel HIIE exercise protocol with adults with asthma. The results show that adults with asthma are able to perform a novel supra-maximal, 140%, HIIE, with similar responses in pulmonary function and markers of airway inflammation outcomes when compared to CWR. The results also suggest HIIE is another exercise choice for adults with asthma to improve their fitness without compromising their lung function or causing adverse symptoms. For people with asthma, improvement in fitness has the potential to decrease risk for developing many other chronic health conditions and most importantly, improve disease control.

Future studies, with greater participant numbers, comparing the long term effects of HIIE with CWR exercise protocols on asthma symptoms, quality of life, decreasing the risk of EIB development are needed.

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Appendix A: Consent Form

Participant Information and Consent Form

STUDY TITLE: The Acute Effect of High Intensity Interval Exercise on Pulmonary Function and Exhaled Nitric Oxide in Adults Asthmatics

PROTOCOL / STUDY NUMBER: 11-138

PRINCIPAL INVESTIGATOR: Dr. Scotty Butcher, PhD, School of Physical Therapy, University of Saskatchewan, Saskatoon, Saskatchewan, S7N 0W3 (306)966-1711

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CONTACT PHONE NUMBER: (306) 966-1711

We would like to invite you to take part in a research study that is being run at the Respiratory and Integrative Clinical Exercise Physiology laboratory in Royal University Hospital. Please take the time to read this consent form and if you wish, discuss it with friends, relatives or your study doctor. This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand, or if you would like more information**.** Take as much time as you need to decide whether or not to take part. Your participation in this study is entirely voluntary, so it is up to you to decide whether or not to take part. If you decide to participate, you are still free to withdraw at any time and without giving any reasons for your decision. If you do not wish to participate, you will not affect your care or academic standing.

Introduction

You are being invited to take part in this research study because you are 18 – 45 years of age and either have or have never been diagnosed with asthma. We are expecting to enroll 15 asthmatics and 15 non asthmatics in this research study. Please feel free to ask the study investigator or research staff any questions that will help you understand the study and what you are expected to do. Before you agree to take part in this study, you may take this information home and discuss it with a family member or your family doctor.

Purpose of the Study

We are studying the nature of breathing limitations with two different exercise protocols in healthy and asthmatic adults. Recent evidence suggests that asthmatics have more breathing difficulties than their healthy peers during the traditional constant work rate exercise. By using a different high intensity interval exercise protocol we may be able to reduce breathing limitations for asthmatics.

Study Visits and Procedures

Main Study:

The study doctor or staff will carefully explain all procedures and you should ask whenever you need more information. You must provide consent to participate in this study before you perform any study-related procedures. You will be scheduled to attend the laboratory on 6 occasions over a period of up to 4 weeks. These scheduled visits will be one to two days apart. At each visit you will be required to perform breathing and exercise tests. You will be asked to avoid consuming caffeine-containing products (e.g. coffee, tea, chocolate) for 4 hours and strenuous activity (e.g. cycling, running) for 12 hours before visits. A normal mixed diet, as outlined by the Canadian Food Guide, should be eaten prior to your visits to the laboratory. These dietary controls are important in allowing us to obtain valid experimental results. You will be asked to not use short-acting B_2-agonists (ie. Ventolin, Bricanyl) for 4 hours before each visit, inhaled anitcholinergics (ie. Atrovent) for 10 hours. You may not be on many of these medications, but if you feel the need to use any of these medications within these time periods you should use them without hesitation, and we will just re-schedule your visit.

As a participant in the study, you will be asked to complete the following procedures:

Visit 1: You will be asked to attend a screening visit, which will last about 1.5 hours. At this visit the study staff will check whether you are suitable for the study: you will be asked some questions about your medical history and the medicines you are using; you will have a general health check up which will include blood pressure measurements. You will be asked to some breathing tests and undergo a methacholine challenge test. This is a standard, widely used test, which assists researchers and doctors in the assessment and severity of airway responsiveness.

Visit 2: This visit will last about 1 hour. During this visit you will be asked to do some breathing tests and you will be asked to exercise on a stationary bicycle for as long as you can. While you are cycling, it will become increasingly harder to cycle – it will feel similar to cycling up a hill that gradually gets steeper and steeper. We will measure your breathing by having you breathe through a mouthpiece while wearing nose clips. We will ask you to breathe deeply periodically throughout the test.

Visit 3 and 5: (tests will be performed in random order). These visits will last approximately 3 hours each. You will be asked to perform two exercise tests on a stationary bicycle for 20 minutes each or till you cannot go any longer. One test will be a constant resistance exercise tests and the other exercise test will be a high intensity interval trial. The high intensity of the interval trial will consist of alternating periods of high and low intensities. During both visits we

will measure your breathing with a mouthpiece and nose clips. We will ask you to breathe deeply periodically throughout the test. During each test, we will measure your oxygen levels and heart rate. You will also be asked to pick a number on a scale that describes how breathless and how fatigued you feel. Prior to each test you will perform breathing tests similar to those performed on Visit 1.

In order to measure breathing mechanics, we will ask to insert a balloon catheter through your nose into your esophagus. You will be asked to sit in a comfortable chair and the back of your nose and throat will be sprayed with a local anesthetic (similar to the anesthetic used when you have dental work). A balloon catheter, which is much like a thin piece of spaghetti, will then be passed through the nose and swallowed into your stomach by sipping water through a straw. The catheter will be withdrawn slightly to position it accurately and it will be held in place by small bits of tape attached to your nose and cheek.

Visit 4 and 6: These visits will be 24 hours after the exercise trials (i.e. third and fifth visits accordingly). The visits will last about 30 minutes and exhaled nitric oxide and breathing tests will be performed.

Sub-study:

In addition to the above procedures, participants who have been diagnosed with asthma will be asked to participate in a sub-study involving the use of standard, preventative bronchodilation therapy on the responses and exercise protocols above. You may choose to participate in the main study and not this sub-study. This sub-study will involve 2 additional visits to the laboratory. These visits will follow the exact same procedures as Visits 3 and 5 above, with the exception that participants will be asked to inhale a common fast acting bronchodilator (Ventolin/Salbutamol) 20 minutes prior to the exercise tests. On one of the visits, participants will be asked to perform the high-intensity interval protocol and on the other visits, participants will be asked to perform the constant work rate protocol. These 2 extra visits will be randomized with Visits 3 and 5 of the main study. These two extra visits will not require the two visits subsequent to the exercise visits (ie. Visits 4 and 6 of the main study).

Breathing Tests: You will be asked to perform several routine lung function tests that are widely used in the assessment of lung function. For most of the tests, you will be asked to breathe through a rubber mouthpiece with your nose clipped. Each test will be repeated 3 – 4 times until results are consistent. During one series of tests, you will be asked to breathe all the way in before blowing out for as long as you can: in one set of tests you will blow all the way out slowly, in the other set of tests you will blow out as hard and as fast as you can. In another test, you will gently "pant" through a mouthpiece while sitting inside a closed chamber; the air during panting will at first move through the mouthpiece, then will be blocked for a few seconds while you make small efforts to pant with no movement of air. During another breathing test you will be asked to remove your nose clips and take a deep breath in and blow out at a constant speed into a machine that will measure your exhaled nitric oxide levels.

Exercise Tests: While breathing through a rubber mouthpiece wearing nose clips, you will be asked to perform several exercise tests consisting of cycling to an endpoint of fatigue, shortness of breath or any other discomfort for which you may need to stop. If, at any time during the exercise tests, you do not wish to continue for any reason, you may stop exercising voluntarily. During and after the testing, you will be asked to rate your breathlessness on a simple questionnaire. At the end of each exercise test, you will be asked the reason you stopped the exercise and to choose phrases from a list which best describes your breathlessness and leg fatigue.

Methacholine Challenge: This is a standard test that assists researchers and doctors in the assessment and severity of airway responsiveness. Methacholine is a substance that will cause your airways to narrow, i.e. bronchoconstrict. You will begin the challenge perform breathing tests described above at least three times. Next you will inhale methacholine by having a facemask placed over your nose and mouth for 2 minutes while you breathe normally. The concentration of methacholine you inhale will increase until your forced expiratory volume in 1 second decreases 20%. During this test you may feel chest tightness, shortness of breath or cough; however, these symptoms are short-lived and can be resolved on their own or after treatment with a bronchodilator.

Exhaled Nitric Oxide Measurement: The measurement of eNO allows researchers and doctors in the assessment and severity of airway inflammation. The higher the eNO level the greater the amount of inflammation. This test will require you to take a deep breath in followed by breathing into a small portable machine at a constant rate until your lungs are empty. This test will be repeated 3 times.

Benefits Associated with the Study
You will not have a direct personal benefit from participation in this study, but you will be contributing to our understanding of how asthmatics experience breathing limitations. In addition, you will be provided with your individual results if requested.

Potential Risk and Discomforts
As with any type of strenuous activity, there is a very small risk that the stress of performing exercise will cause heart rhythm abnormalities, chest discomfort or light headedness. People with a history or presence of significant cardiac (heart) disease or heart rhythm disorders should not participate in this study. The study doctor may decide that you should not perform the exercise tests, based on information in your medical history. ***It is important that you let the study investigator or staff know if you have ever been advised not to participate in strenuous activities***. It is also important that you report any pain, discomfort, fatigue or other symptoms that you might have during the exercise test to the physician in attendance.

During the performance of the breathing tests, major discomfort is unusual. However, you may experience mild light-headedness or breathlessness, or you may cough or wheeze at the end of some of the breathing tests, but these sensations subside as soon as the test is stopped for a few moments. People who have had a recent heart attack, recent eye or abdominal

surgery, or any history of coughing up significant amounts of blood in the previous 6 months will not be asked to undergo these tests. Insertion of the balloon catheter presents minor risks which could include: discomfort on insertion of the catheter, minor nasal trauma (nose bleed), gagging or vomiting.

Risks of the study are related to the measurements being performed (see above). Risks and discomforts will be minimized by preliminary screening and examination, by observations made throughout the study, and through close access to emergency equipment and medical personnel. You will be carefully monitored throughout testing and a physician will be immediately available in case problems should arise. All tests will be performed by staff who are trained to deal with problems that may arise. At any time during the study, it is important that you tell the study doctor if you feel unwell or experience any problems or side effects. It is usual to experience some degree of muscle discomfort during the tests described above. This discomfort should be temporary. Your muscles may feel sore for a couple of days after each test. This soreness is expected due to the testing procedures and should subside quickly. If you are concerned about the amount of soreness, let the study staff know.

Methacholine is routinely used in clinical practice and in research for assessing airway responsiveness. Methacholine is a registered product (Provocholine®) and as such is approved for use in Canada by the Therapeutic Products Directorate of Health Canada. Possible side effects from inhaling methacholine include coughing, chest tightness, shortness of breath or wheezing. Rarely, symptoms may include headache, itching, throat irritation or light headedness. Any symptoms are usually very quickly relieved after stopping the test or with the use of a bronchodilator. You should let the study staff and/or doctor know if you experience any of these symptoms during this test.

Ventolin is routinely used in clinical practice and in research for achieving bronchodilation in patients with airway constriction. Ventolin is a registered product (Salbutamol®) and as such is approved for use in Canada by the Therapeutic Products Directorate of Health Canada. Possible side effects from inhaling ventolin include coughing, difficulty sleeping, dry or irritated throat, faster heartbeat (usually temporary), flushing, headache, irritability, nausea, nervousness, restlessness, tremor (shakiness), or viral infections of the nose and throat (fever, sore throat, runny nose). Any symptoms are usually temporary and very quickly relieved. You should let the study staff and/or doctor know if you experience any of these symptoms during your visits.

If you are pregnant or are currently breastfeeding, you will not be allowed to participate in this study. You should also avoid becoming pregnant during this study. Although methacholine challenge testing are not contraindicated during pregnancy or while breastfeeding it is an unnecessary exposure and as such will be avoided. A urine pregnancy test will be conducted at the start of each treatment period to ensure you are not pregnant.

Research-Related Injury

There will be no costs to you for participation in this study. You will not be charged for any research procedures. In the event that you become ill or injured as a result of participating in

this study, necessary medical treatment will be made available at no additional cost to you. By signing this document you do not waive any of your legal rights.

Voluntary Participation and Withdrawal

Your participation in this study is voluntary and you may choose not to participate or withdraw from the study, at any time, without penalty or loss of benefits to which you are otherwise entitled. If you do not wish to participate or if you withdraw from the study, neither your current nor future medical care will be adversely affected. If you agree to participate in the trial, the study staff will ensure, with your agreement, that your family doctor is informed about your participation. The study investigator or doctor may also remove you from the study at any time if it is decided that it is not in the best interest of the study and/or your health to continue, or if you do not follow the study staff's instructions.

If you develop a problem that requires medical attention, you should seek emergency medical treatment, and then contact the study doctor immediately.

Payment to Participants

You will not be paid for taking part in the study. There will be no charge to you for any tests done as part of the study.

Confidentiality

Your confidentiality will be respected. No information that discloses your identity will be released or published without your specific consent to the disclosure. However, research records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of University of Saskatchewan Research Ethics Board for the purpose of monitoring the research. However, no records, which identify you by name or initials, will be allowed to leave the Investigators' offices.

The results of this study may be presented in a scientific meeting or published, but your identity will not be disclosed.

Further Information

You may contact Dr. Scotty Butcher, at (306)966-1711 for side effects, questions, or concerns. For medical emergencies, please go to a hospital emergency room. You have the right at any time to request information from the study staff about your condition. You may also request that any other person, including your personal doctor, be given this information and a copy of this form.

The study has been reviewed and approved by the University of Saskatchewan Biomedical Research Ethics Board. They are responsible for safeguarding the safety, rights and well-being of human participants participating in research studies. For additional information regarding your rights as a research participant or concerns about the study, contact the Chair of the Biomedical Research Ethics Board, c/o the Ethics Office, University of Saskatchewan at (306)966-4053.

If you have any questions during the study, or if you experience any side effects, please contact:

Dr. Scott Butcher (Principal Investigator): (306) 966-1711
Please take a copy of this form home with you.

The Acute Effect of High Intensity Interval Exercise on Pulmonary Function and Exhaled Nitric Oxide in Adults Asthmatics

CONSENT FORM

I have read and I understand the information presented in this form.
I have had the purpose, procedures and technical language of this study fully explained to me. I have been given sufficient time and opportunity to consider the above information, to inquire about details of the study and to decide whether or not to participate.
Having read all pages of this information and consent form and understanding the requirements of the study, my signature below indicates that I voluntarily consent to participate in this study.
I understand that I will receive a copy of this information and consent form.

Please check the appropriate statement to indicate your decision:
_____ My family physician **can be** informed about my participation in this study, and, if required, consulted regarding my health and treatment.
or
_____ My family physician **cannot be** informed about my participation in this study, and, if required, consulted regarding my health and treatment.
or
_____ I do not have a family physician.

_____
Participant Name (print name)

_____
Signature of Participant Date

I, or one of my colleagues, have carefully explained to the participant, the nature of the above research study. I certify that, to the best of my knowledge, the participant clearly understands the nature of the study and the demands, benefits and risks involved in participating in the study.

_____
Investigator (or Designee) Name (please print)

_____ _____
Investigator (or Designee) Signature Date

Appendix B: Day 1 Data Sheet

Name:
Height: **Weight(kg):**
Gender: M - F
DOB(Da/Mo/Yr)
Medical Background: Healthy - Asthma

Exclusion criteria for asthmics:

- **tidal breathing methacholine provocation concentration to cause a 20% decrease in FEV_1 (PC_{20}) > 16 mg/ml**
- **FEV_1 < 65% predicted**
- **Respiratory tract infection or allergen exposure for ≥ 4 weeks**

Exclusion criteria for both groups include:

- **chronic or acute cardiac, metabolic, neuromuscular illness**
- **musculoskeletal illness or injury that would limit their ability to perform heavy exercise**

Medications & Dosages

Exercise Background (aerobic and strength)

Have you done any of the following…..

- ❑ No strenuous activity within 12 hours of test
- ❑ No alcohol, caffeine within 4 hours of test
- ❑ No short acting B_2-agonists (ie. Ventolin, Bricanyl) for 4 hours before each visit
- ❑ No inhaled anticholinergics (ie. Atrovent) for 10 hours

eNO (ppb) (within 10%)
1 _____ 2_____ 3_____ Avg:_____

Baseline Spirometry (attach printout)
FEV_1_____ FEV_1 _____ FEV_1 _____
% Pre_____ % Pre _____ % Pre _____
Methacholine – time inhaled = 2min

Concentration	30 sec FEV_1	90 sec FEV_1	% ↓ FEV_1
Diluent			
PC_{20} =			

Calculations

Appendix C: Day 2 Datasheet

Pulmonary Function Tests – Best Values	
FEV_1	
% Pred	
TLC	
RV	
DLCO	
DLCO/VA	
R_{AW}	
Print out PFT 1 page	

VO_2 Max Test

Max Watts VO2 Max _____

RPM _____

Print out Cardiopulmonary Exercise Test Results

5 min 50 W warm up protocol.

Ex Time	Blood Pressure	RPE		IC	Heart Rate
		SOB	Legs	(Ö)	
RESTING					
0:00					
0:30					
1:00					
1:30					
2:00					
2:30					
3:00					
3:30					
4:00					
4:30					
5:00					
5:30					
6:00					
6:30					
7:00					
7:30					
8:00					
8:30					
9:00					
9:30					
10:00					
10:30					
11:00					
11:30					
12:00					
12:30					
13:00					
13:30					
14:00					
14:30					
15:00					
ENDING					

Why did you stop?

Appendix D: CWR Data Sheet

CWR

Name: _____ Subject #:_____

Age: _____ Weight:_____ Height: _____

OW 1 min WU 60% of Max Watts VO2max:_____

Time	RPE		IC (√)	Heart Rate
	SOB	Legs		
Resting				
0:00				
0:30				
1:00				
1:30				
2:00				
2:30				
3:00				
3:30				
4:00				
4:30				
5:00				
5:30				
6:00				
6:30				
7:00				
7:30				
8:00				
8:30				
9:00				
9:30				
10:00				
10:30				
11:00				
11:30				

12:00				
12:30				
13:00				
END				

Why did you stop?

Appendix E: HIIE Datasheet

HIIE

Name: _____ **Subject #:** _____

20% Max Watts VO2max: _____ 140% Max Watts of VO2max:_____

5 min unloaded warmup in protocol.

Ex Time	Blood Pressure	RPE		IC	Heart Rate
		SOB	Legs	(√)	
RESTING					
0:00					
0:30					
1:00					
1:30					
2:00					
2:30					
3:00					
3:30					
4:00					
4:30					
5:00					
5:30					
6:00					
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12:30					
13:00					
13:30					
14:00					
14:30					
15:00					
15:30					
16:00					
16:30					
17:00					
17:30					
18:00					
18:30					
19:00					
19:30					
20:00					
ENDING					

Appendix F: Day 3 and 4 Datasheet

Day 3 or 4 – Exercise Days Subject ID: 11-138
Date: Location

□ No strenuous activity within 12 hours of test
□ No alcohol, caffeine within 4 hours of test
□ Any medications? Yes No
□ If yes, which? When?

1. Baseline eNO (ppb) (within 10%)

1 2 3 avg

2. Spirotmetry

FEV_1 FEV_1 FEV_1
% pred %pred %pred
FVC FVC FVC

3. Plethysmography

TLC R_{AW}

PRINT OUT PFT ALL TRIALS AND 1 PAGE PFT REPORT

4. ECG Leads on

5. Balloon Insertion

6. Exercise CWR HIIE
    a. 2 min resting data
    b. 5 min warm up
    c. Exercise 20 min or tolerance
    d. 5 min cool down

7. Balloon out

8. Post exercise

eNO (ppb)						
1		2		3	avg	
Time Post Exercise (min)	Time (h:min)	FEV1 (L)	FEV1	FEV1	TLC	R_{AW}
0						
5					[redacted]	
10						
15						
20						
30						

Appendix G: During Exercise Graphs

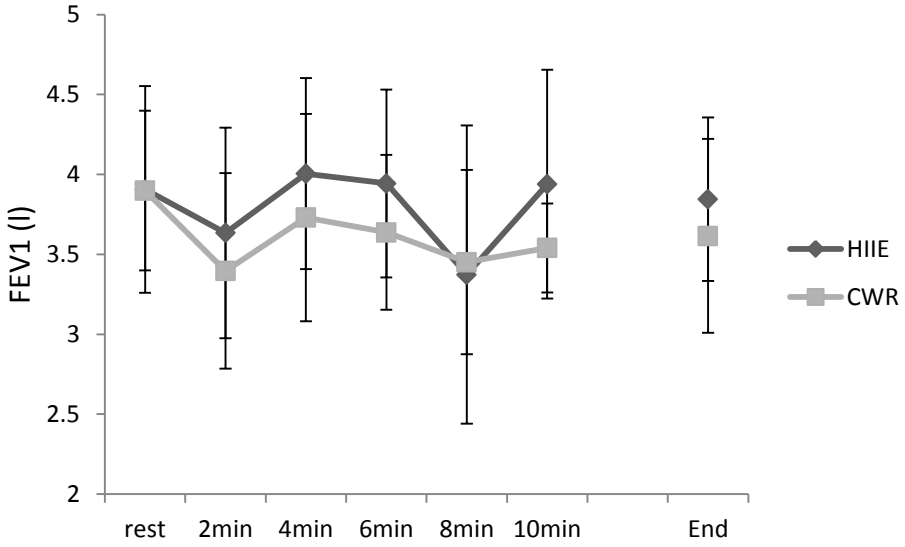

Figure A-1: FEV_1 vs. time up to 10 minutes and end for both exercise protocols. Mean values are plotted. No significant differences seen in FEV_1 between exercise protocols at any time point, $p > 0.05$. Values are in liters. High Intensity Interval Exercise (HIIE) and Constant Work Rate (CWR).

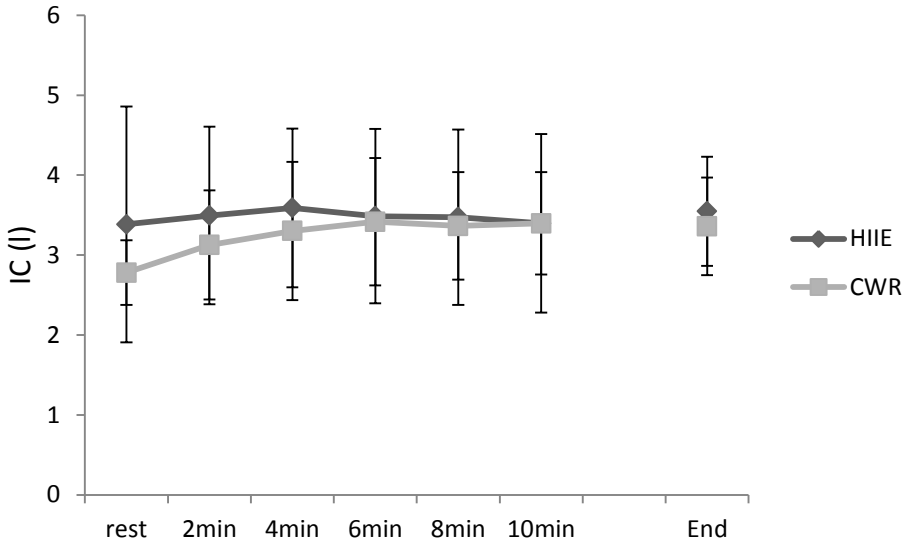

Figure A-2: IC vs. time up to 10 minutes and end for both exercise protocols. Mean values are plotted. Values are in litres. No significant differences seen in ICs between exercise protocols at any time point, $p>0.05$. High Intensity Interval Exercise (HIIE) and Constant Work Rate (CWR).