The Acute Response to High Intensity Interval Exercise in Adults with Exercise Induced Bronchoconstriction

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ABSTRACT

INTRODUCTION: Exercise induced bronchoconstriction (EIBC) occurs as a result of airway cooling and drying in adults with airway hyperresponsiveness (AHR). Continuous exercise leads to a significant decline in lung function; however, interval exercise may allow ventilation to recover and prevent EIBC. PURPOSE: To determine the acute response of lung function and the subjective perceptions during and after a bout of high intensity interval (HIIE), moderate intensity interval (MIIE), and moderate intensity continuous (MICE) exercise in adults with AHR. METHODS: Participants completed an acute bout of HIIE, MIIE, and MICE. Lung function was assessed pre and post-exercise while late phase symptoms were reported using a log and subjective responses were assessed during each minute of exercise. RESULTS: Thirteen participants with EIBC completed all protocols. Lung function was significantly lower following the MICE and perceptions of effort and dyspnea were higher. CONCLUSION: It appears HIIE is well tolerated among adults with AHR.

KEYWORDS: Bronchoconstriction, High Intensity Interval Exercise, Lung Function, Affect, Perceived Exertion, Perceived Dyspnea

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LIST OF ABBREVIATIONS

ACOS Asthma-chronic obstructive pulmonary disease overlap syndrome

AHR Airway Hyper-responsiveness

CF Cystic Fibrosis

COPD Chronic obstructive pulmonary disorder

EIBC Exercise induced bronchoconstriction

EVH Eucapnic voluntary hypernea

FeNO Fractional exhaled nitric oxide

FEV_1 Forced expiratory volume in 1 second

FS One item feelings scale

FVC Forced vital capacity

HIIE High intensity interval exercise

HIIT High intensity interval training

MICE Moderate intensity continuous exercise

MIIE Moderate intensity interval exercise

RPD Ratings of perceived dyspnea

RPE Ratings of perceived exertion

PACES Physical activity enjoyment scale

PPO Peak power output

VO_{2max} Maximal oxygen consumption

CHAPTER 1: INTRODUCTION

1.1 THESIS INTRODUCTION

Airway hyperresponsiveness (AHR) is defined as an increased sensitivity of the airways and is a characteristic feature of asthma (O'Byrne & Inman, 2003). Among those with AHR, exercise is a trigger for acute bronchoconstriction in adults with AHR, with approximately 90% of adults with AHR experiencing exercise-induced bronchoconstriction (EIBC) (Weiler, Whipp, Koyl, & Beaver, 2007). EIBC has been suggested to occur due to an increase in heat and evaporative water loss from the airways as a result of high ventilations, which is typically experienced during aerobic exercise. Given that exercise is a trigger for the majority of adults with AHR, it is not surprising that physical activity rates among this population are suboptimal (Ford, Heath, Mannino, & Redd, 2003). However, research suggests that in addition to the well-established benefits of exercise, such as improved cardiovascular health, decreased risk of chronic conditions, and improvements in psychological well-being, regular exercise among adults with AHR can improve asthma symptoms and improve asthma control (Dogra, Kuk, Baker, & Jamnik, 2011). Therefore, it is crucial to determine the optimal form of exercise for this population in order to increase exercise adherence and improve overall health and asthma related symptoms among this population.

High intensity interval exercise (HIIE) includes brief bouts of high intensity exercise followed by intermittent recovery periods. HIIE has been shown to be an effective form of exercise among patients with various chronic conditions; unfortunately, HIIE has not yet been studied among those with EIBC. However, there are components of HIIE that provide promise for its tolerability and successful implementation among adults with EIBC. For example, the intermittent recovery periods associated with HIIE may allow for ventilation to recover and thus reduce the amount of water and heat loss from the airways. Additionally, these recovery periods may allow time for adults with AHR to 'catch their breath', which may reduce perceptions of dyspnea typically experienced during exercise. The potential for HIIE to allow ventilation to recover and reduce perceptions of dyspnea may lead to greater exercise affect and enjoyment. This is particularly important given that research suggests that positive exercise affect can predict future exercise engagement (Williams et al., 2008); therefore, in order to increase exercise adherence among this population it is necessary to determine a form of exercise that elicits physiological benefits while providing a positive psychological experience.

1.2 RESEARCH OBJECTIVES AND HYPOTHESIS

Objective 1:

Determine changes in lung function and onset of late phase asthma symptoms following an acute bout of HIIE, MIIE and MICE among adults with confirmed EIBC.

Hypothesis: Interval exercise will allow ventilation to recover intermittently and thus, preserve lung function which may therefore reduce late phase asthma symptoms as compared to MICE.

Objective 2:

Determine the subjective response of exertion, dyspnea, affect, and overall physical activity enjoyment during and following a single session of HIIE, MIIE, and MICE among adults with confirmed EIBC.

Hypothesis: It is hypothesized that MIIE will elicit the lowest perceptions of effort and dyspnea but the greatest enjoyment due to the moderate intensity nature paired with recovery intervals. Further, due to the high intensity nature and intermittent recovery periods associated with HIIE, it is hypothesized that HIIE will elicit higher perceptions of exertion; however, will elicit lower perceptions of dyspnea, greater affect, and overall greater physical activity enjoyment as compared to MICE.

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CHAPTER 2: REVIEW OF THE LITERATURE

Literature Review

The following literature review will highlight evidence relevant to the pathogenesis and diagnosis of exercise induced bronchoconstriction (EIBC), common asthma management techniques, asthma comorbidities and the role of exercise intensity in EIBC.

2.1 PATHOGENESIS AND DIAGNOSIS OF EXERCISE INDUCED BRONCHOCONSTRICTION

Asthma is characterized by chronic inflammation and acute bronchoconstriction. Asthma can be subdivided into atopic and non-atopic asthma. The atopic type is distinguished from the non-atopic type based on a family history of allergies, high serum IgE, and by a positive skin prick test. Although patients with both types of asthma experience airway hyper-responsiveness (AHR) it is possible that the mechanisms responsible for AHR in non-atopic asthma may be different than that of atopic asthma (Mochizuki, Shigeta, Tokuyama, & Morikawa, 1999). Chronic inflammation in both types of asthma is due to the release of numerous cytokines and inflammatory markers (Pueringer & Hunninghake, 1992). Acute bronchoconstriction occurs as a result of exposure to a trigger and initiates the release of cytokines and inflammatory markers. Acute bronchonconstriction can be broken down into an early and late phase reaction (Bousquet, Jeffery, Busse, Johnson, & Vignola, 2000). The early phase reaction occurs minutes after exposure to a trigger; whereas, the late phase reaction can occur up to 9 hours after exposure to a trigger and can cause difficulties breathing for up to 24 hours after exposure (Raemdonck et al., 2011). EIBC is characterized by acute airway narrowing that occurs as a result of exercise; however, the exact pathogenesis of EIBC remains unclear. Despite the unclear pathogenesis, it is clear that inflammatory mediators such as histamine, tryptase, and leukotrienes are released into the airways from cellular sources such as eosinophils and mast cells as a result of exercise (Hallstrand et al., 2005; Mickleborough, Lindley, & Ray, 2005).

Although the pathogenesis of EIBC is unclear, two hypotheses have been suggested to explain EIBC, the osmotic and the thermal hypothesis. The osmotic hypothesis suggests that the increase in water loss in the airways that occurs as a result of an increase in ventilation triggers EIBC. The thermal hypothesis suggests that the cooling of the airways as a result of an increase in ventilation, followed by the subsequent rewarming of the airways following exercise (reactive hyperemia) is what triggers the EIBC response (Anderson, 2006). In a review of both hypotheses it was suggested that EIBC likely occurs as a result of both the osmotic and thermal hypothesis (Anderson & Daviskas, 2000). Additionally, it has been suggested that the epithelium may play a key role in sensing the transfer of water and heat out of the airways, but how this epithelial response triggers cellular activation by leukocytes remains unclear (Parsons et al., 2012). Due to the unclear pathogenesis of EIBC, studies have shown that EIBC is commonly under-diagnosed. Specifically, in a study examining the under-diagnosis of asthma in young adults presenting for basic training for the United States Air Force, participants were screened for asthma through a medical history, physical examination, pulmonary function tests and by histamine or exercise challenge tests. It was found that of those diagnosed with asthma, 30% of participants had not been previously diagnosed and that EIBC accounted for most of the undiagnosed asthma (Nish & Schwietz, 1992).

One tool commonly used to assess lung function and assess asthma severity is spirometry. Spirometry measures parameters of lung function such as, forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). In a normal airway, the ratio of these parameters should be greater than 80%; a ratio less than 80% indicates an obstructive lung disease such as asthma (D'Urzo, Tamari, Bouchard, Jhirad, & Jugovic, 2011). The severity of EIBC can be assessed using spirometry by evaluating the percent decline in FEV_1 from pre to post exercise. The severity of EIBC is graded as mild, moderate and severe if the percent fall in FEV_1 from baseline is >10% but <25%, >25% but <50%, and >50% respectively (Parsons et al., 2012). Spirometry is an invaluable screening test for lung function; therefore, in order to minimize variability of the results and to improve measurement accuracy standardized guidelines have been developed by the American Thoracic Society (Miller et al., 2005).

The most effective confirmation test for EIBC is the indirect eucapnic voluntary hyperpnea (EVH) challenge. The EVH challenge is a sensitive and specific diagnostic method that triggers EIBC by hyperventilation of safe concentrations of dry gases that simulate ventilation for a period of 6 minutes. Prior to the EVH challenge participants are asked to refrain from taking short acting bronchodilators for 8 hours and to refrain from taking long acting or sustained release bronchodilators for 48 hours. This is done in order to maximize the airway response. Prior to the EVH challenge, lung function is measured three times and the highest measurement is used to calculate the airway response. Lung function is assessed again following the challenge at minutes 5, 10, 15 and 20-post challenge test (Parsons et al., 2012). The percent decline between the FEV_1 obtained pre challenge and the FEV_1 obtained post challenge is used to determine the airway response. A decline in FEV_1 of 10% or greater is indicative of EIBC. The EVH challenge has a very high sensitivity and is recommended by the International Olympic Committee-Medical Commission (Holzer & Brukner, 2004; Dickinson, Whyte, McConnell, & Harries, 2006). Thousands of EVH challenges have been performed without serious unwanted side effects, making it a safe and effective diagnostic tool (Deal, McFadden, Ingram, Breslin, & Jaeger, 1980; Weiss et al., 1984).

The EVH challenge is considered to provoke a more potent EIBC response than exercise challenges; however, exercise challenge tests are commonly employed to determine EIBC when the EVH is unavailable (Mannix, Mandredi, & Farber, 1999; Eliasson, Phillips, & Rajagopal, 1992). Additionally, among athletic participants who express a negative response to the EVH it is recommended to perform a sports-specific EIBC exercise challenge test under the conditions that reproduce the participants symptoms (Rundell et al., 2000; Mannix, Farber, Palange, Galassetti, & Manfredi, 1996). Exercise challenge protocols have been standardized for treadmill and cycle ergometer tests (Roca et al., 1997). Briefly, the general principle for these challenges is to have the participant exercise at an intensity intense enough that only 6-8 minutes of exercise is required to provoke EIBC. The recommended intensity for challenges using a treadmill is an intensity that allows ventilation to be raised and sustained, for approximately 4 minutes, above 17 to 21 times FEV_1 and heart rate to 80-90% of maximal (Carlsen, Engh, & Mork, 2000). If a treadmill is unavailable for testing or, if the participant is unable to exercise on a treadmill an exercise challenge test can be conducted using a cycle ergometer. Generally, for exercise tests on a cycle ergometer the workload is set to 60% of the target workload during the first minute and continues to progress in intensity to 70%, 90%, and 100% for the second, third, and fourth minutes respectively. Once the target workload is reached ventilation rates are checked and the participant is encouraged to maintain the exercise intensity for 4 minutes. Following an exercise challenge lung function is assessed post-exercise at various time intervals. It is advised that FEV_1 be measured immediately following exercise and continue to be measured for 20-30 minutes post, as FEV_1 can occasionally fall as late as 20-30 minutes post exercise (Brudno, Wagner, & Rupp, 1994).

It is clear from the literature that EIBC occurs in the vast majority of adults with asthma through mechanisms that are not completely understood. This lack of understanding leads to an under-diagnosis of the condition; however, diagnostic tools such as the EVH and exercise challenge tests have been developed and standardized in order to more effectively diagnose EIBC.

2.2 EIBC MANAGEMENT

Currently, there is no cure for asthma; however, a variety of management techniques are commonly used to control the disease. These management techniques include a combination of pharmacological agents and regular physical activity.

Pharmacological Agents

Corticosteroids are the most commonly prescribed medication to treat the chronic inflammation associated with asthma. Corticosteroids predominately treat the inflammation associated with asthma through switching off multiple inflammatory genes such as cytokines, adhesion molecules, and inflammatory enzymes (Barnes, 1994; Barnes, Chung, & Adcock, 1995). Specifically, the process of the induction of chronic cytokine expression and the activation of inflammatory cells in asthma involve an increase in the transcription of inflammatory genes. This is regulated by transcription factors such as nuclear factor $_k$B, which are located in the promoter region of inflammatory genes (Barnes & Adcock, 1996; Hart, Krishnan, Adcock, Barnes, & Chung, 1998). Corticosteroids diffuse readily across cell membranes and bind to glucocorticoid receptors in the cytoplasm which translocate to the nucleus where they binds to corticosteroid responsive genes known as glucocorticoid response elements. These may encode anti-inflammatory proteins (Dostert & Heinzel, 2004). Corticosteroids are typically prescribed to be taken daily and can control disease symptoms through regular adherence (Sumino & Cabana, 2013).

Acute bronchoconstriction is typically treated with short acting $beta_2$ adrenergic receptor agonists, commonly referred to as reliever or rescue medication. These medications are taken upon the onset of asthma symptoms or can be taken prior to coming into contact with a trigger for example, prior to exercise. $Beta_2$ - agonists act as a bronchodilator and can be short or long lasting. The long lasting class of this medication allows for protection from bronchoconstriction for up to 12 hours. $Beta_2$-agonists act mainly to relax smooth muscle by stimulating $beta_2$-receptors; this increases cyclic adenosine monophosphate (a second messenger) and produces functional antagonism to bronchoconstriction. Additionally, $beta_2$-agonists may also have anti-inflammatory properties (Sinn, McAlister, Man, & Anthonisen, 2003). Often, long acting bronchodilators are combined with inhaled corticosteroids into one inhaler. This is referred to as combination therapy; however, medication prescription varies from patient to patient (Bateman et al., 2008).

Despite the evidence surrounding the effectiveness of both corticosteroids and bronchodilators, there is poor adherence to medication in individuals with asthma (Laforest et al., 2006). Many individuals feel that when they are not experiencing symptoms, they do not need to take medication; however, this is not the case (Blaiss et al., 2009). Corticosteroids must be taken on a regular basis in order to work effectively. Additionally, many individuals with asthma fail to regularly adhere to their medication out of concern for side effects. For example, long term use of inhaled corticosteroids has the potential to cause impaired growth in children and decreased bone mineral density; however, it should be noted that these side effects are rare and occur as a result of high doses of corticosteroids (Dahl, 2006). Common side effects of beta 2-agonists include skeletal muscle tremors and tachycardia; however, these effects are infrequent and typically occur at a mild degree. These side effects are also generally outweighed by the improvements in asthma control that occur following regular adherence to a beta 2-agonists (Lulich, Goldie, Ryan, & Paterson, 1986). Specifically, in a survey of 603 Canadians with asthma, more than half reported being very or somewhat concerned about using inhaled corticosteroids on a regular basis. However, these concerns stem from misunderstanding and lack of asthma education surrounding their medication use (Boulet, 1989). These misconceptions about medication use lead to a lack of adherence to medication, which greatly affects the healthcare system (Iskedijian, Addis, & Einarson, 2002).

Thus, pharmacological agents play a critical role in the prevention and treatment of asthma and EIBC. Unfortunately, adherence rates remain low; therefore, efforts need to be made to increase medication adherence to allow adults with asthma to exercise with minimal symptoms and improve asthma control, physical fitness, and potentially reduce medication needs.

Physical Activity

In addition to prescribed medication, regular physical activity has been shown to improve asthma control, asthma symptoms, quality of life and parameters of lung function in addition to exercise capacity (Abmaidi, Varray, Savy-Pacaux, & Prefaut, 1993; Basaran et al., 2006; Shaw & Shaw, 2011).

Whether there is an improvement in lung function as a result of regular exercise in individuals with asthma remains inconclusive (Shaw & Shaw, 2011; Chandratileke et al., 2012). In a study by Shaw and Shaw (2011), an 8-week aerobic exercise intervention in 22 individuals with asthma was conducted. The aerobic training intervention consisted mainly of walking and jogging. Following the 8-week intervention improvements in FVC, FEV_1, and peak expiratory flow were observed (Shaw & Shaw, 2011). Further, in a recent systematic review of the effects of exercise training on airway hyper reactivity, it was found that FEV_1 improved following adherence to various exercise training programs (Eichenberger, Diener, Kofmehl, & Spengler, 2013). On the contrary, in a meta-analysis on the effects of physical activity among individuals with asthma, no significant improvements in FEV_1 were observed (Chandratileke et al., 2012). Furthermore, several intervention studies have shown that lung function does not improve with regular exercise (Dogra, Kuk, Baker, & Jamnik, 2011; Meyer, Gunther, Volmer, Taube, & Baumann, 2015). The noted discrepancies concerning the effects of exercise training on lung function (i.e. asthma severity) in individuals with asthma may be due to differences in subjects, type of training, duration of training, and severity of asthma diagnoses. These inconsistencies require further investigation in order to elucidate the effects of regular exercise on lung function in adults with asthma.

Asthma control and quality of life have been examined in a variety of studies; however, inconsistent tools of measurement have made it difficult to make definitive conclusions about the level of effectiveness of physical activity in improving asthma control and quality of life. Nevertheless, significant improvements have been observed in asthma control and quality of life following a 12-week exercise intervention in adults with asthma (Dogra et al., 2011). Similarly, following a 12-month exercise intervention consisting of 60-minute sessions once per week, improvements were noted in most of the quality of life domains (Meyer et al., 2015). Further, improvements in the psychosocial domain of health have been observed following a 12-week aerobic exercise training intervention. Specifically, improvements in depression and anxiety levels significantly improved following exercise training (Mendes et al., 2010). Similar improvements in fear and anxiety about exercise were observed in a 10-week rehabilitation study. In this study, adults with mild to moderate asthma exercised twice a week in a pool at a high intensity. Following the exercise program participants were less afraid of experiencing breathlessness during exercise and were less anxious about exercising at a high intensity (Emtner, Herala, & Stalenheim, 1996). Additionally, a reduction in short-acting beta$_2$-agonist medication has been observed following an 8-week aerobic exercise intervention (Bundgaard et al., 1983).

The aforementioned studies illustrate the benefits of regular aerobic exercise for improving asthma control as well as improving components of health. Therefore, efforts to improve adherence to regular exercise among this population not only offers physical health benefits but benefits in the psychosocial health domain as well.

2.3 COMORBIDITIES

Asthma is associated with various comorbidities such as atopy, allergies, obesity and asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS). For the purpose of this review, only those comorbidities most related to the present study will be discussed.

Obesity

Asthma is associated with an increased risk of obesity, which is further associated with greater health complications such as diabetes, depression, and cardiovascular disease and creates a significant burden on the health care system (Withrow & Alter, 2011). Specifically, in an epidemiological study using data from the Canadian Community Health Survey (2005), it was found that obese/inactive individuals with asthma were 95% more likely to have reported an overnight hospital stay in comparison to active/normal weight adults with asthma (Dogra, Baker, & Arden, 2009). Regular exercise promotes weight loss and the maintenance of a healthy body weight; therefore, lowering the risk of obesity. In addition, regular exercise can reduce blood pressure, lower low-density lipoprotein levels (the "bad" cholesterol) in the blood, and increase high-density lipoprotein levels (the "good" cholesterol) in the blood (Myers, 2003).

Traditionally, endurance exercise has been the most popular form of exercise in reducing weight; however, research suggests that high intensity interval training (HIIT) may offer similar and/or superior weight loss reduction with a lesser time commitment. For example, Tremblay and colleagues (1994) compared the effects of a 20-week endurance-training program versus a 15-week HIIT program in young healthy adults. Despite a significantly lesser energy cost at the end of the study, a nine-fold greater reduction in subcutaneous adiposity was observed in the HIIT group (Tremblay, Simoneau, & Bouchard, 1994). Mechanisms of HIIT in combatting obesity include an increase in exercise and post-exercise fat oxidation and a decrease in post-exercise appetite. One study suggested that towards the end of a HIIT session, which consisted of numerous repeat sprints, an inhibition of anaerobic glycogenolysis occurs and adenosine triphosphate re-synthesis is mainly derived from phosphorylated creatine degradation and intramuscular triacylglycerol stores (Gaitanos, Williams, Boobis, & Brooks, 1993). Similarly, in trained and untrained female cyclists, an increase in venous glycerol accompanied HIIT, which supports the notion that acute HIIT progressively results in greater fatty acid transport (Trapp, Chisholm, & Boutcher, 2007). Burgomaster and colleagues also reported a marked increase in skeletal muscle capacity for fatty acid oxidation in 6 HIIT sessions (Burgomaster, Hughes, Heigenhauser, Bradwell, & Gibala, 2005).

The effect of HIIT in reducing weight with a minimal time commitment may minimize barriers, such as lack of time, to regular exercise and may lead to a greater adherence to a weight management/reduction exercise program.

Asthma-COPD Overlap Syndrome

Adults with asthma are also at an increased risk of developing COPD, which typically develops in mid-life or later, and is characterized by an incompletely reversible airflow limitation that results in a progressive decline in lung function (Fabbri et al., 2003). The definitions of asthma and COPD describe the physiological and anatomical extremes, which allows them to be recognized as distinct diseases. However, research has suggested that a re-evaluation of the concept that asthma and COPD are separate conditions is required (Fabbri et al., 2003). Therefore, the Global Initiative for Asthma and the Global Initiative for Chronic Obstructive Lung Disease has characterized the ACOS by "persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features it shares with both asthma and COPD" (Global Initiative for Asthma, 2014). The frequency of ACOS increases with advancing age, with an estimated prevalence of <10% in patients younger than 50 years and >50% in patients aged 80 years or older (Soriano et al., 2003).

The increased risk for obesity and ACOS among adults with asthma is associated with additional health complications and additional burdens to the health care system (Andersen, Lampela, Nevanlinna, Sayajakangas, & High, 2013). Therefore, regular exercise among this population is crucial in order to prevent, manage, and improve disease symptoms.

2.4 EXERCISE INTENSITY

Research on exercise in adults with asthma has primarily focused on moderate intensity continuous exercise (MICE) (Boyd et al., 2012). This type of exercise has been shown to improve physical fitness and quality of life among this population; however, this form of exercise requires a substantial time commitment, which is often considered a barrier to regular exercise among adults with asthma (Mancusco et al., 2006). HIIE is a high intensity form of exercise that requires a much smaller time commitment. The shorter time commitment paired with the physiological gains associated with this type of exercise has led to an increase in popularity of HIIE among healthy and clinical populations.

High Intensity Interval Exercise

HIIE has not yet been studied among adults with EIBC; however, it has been studied among individuals with a variety of chronic conditions, including those with pulmonary conditions such as COPD and cystic fibrosis (CF). There are various properties of HIIE that suggest it may be feasible among adults with EIBC. First, exercise leads to an increase in epinephrine secretion and higher intensity exercise leads to a greater secretion, which has been shown to influence EIBC, as epinephrine binds to $beta_2$ receptors in the airway causing bronchodilation i.e. making it easier to breathe (Trapp et al., 2007). Secondly, lack of time is a significant barrier to regular exercise; however, HIIE requires a lesser time commitment with similar physiological adaptations as traditional endurance training (Gibala, Little, MacDonald, & Hawley, 2012). Unfortunately, HIIE is also associated with an increase in ventilation, which is associated with a higher risk of experiencing EIBC. Therefore, the feasibility of HIIE in adults with EIBC remains unclear and warrants further investigation.

HIIE as a mode of exercise training has not yet been studied among adults with asthma; however interval exercise as a means of warm-up prior to exercise has been examined. Specifically, various studies have compared the decline in FEV_1 after an exercise challenge test following a high intensity interval warm-up versus an exercise challenge test with no warm-up (de Bisschop, Guenard, Desnot, & Vergeret, 1999; McKenzie, McLuckie, & Stirling, 1994; Mickleborough, Lindley, & Turner, 2007; Schnall & Landau, 1980). The interval warm-ups were composed of 26-30 seconds at 100% of maximal oxygen consumption. Results from these studies show an improvement in the drop in FEV_1 ranging from 4.8-16.1% when compared to the no warm up groups. These results suggest that repeated brief bursts of high intensity exercise as a warm-up for traditional continuous exercise appears to improve post-exercise FEV_1; however, the lung function response to HIIE as an exercise bout among adults with EIBC has not yet been studied.

The feasibility of HIIE has been examined in patients with COPD. In a review by Kortianou and colleagues (2010), the effectiveness of interval exercise training in patients with COPD was explored. Through this review it was found that patients with COPD are able to tolerate HIIE. Further, it was found that HIIE leads to improvements in exercise tolerance and quality of life among this population. With regards to the intermittent nature of the exercise, a study examining the physiological response to moderate intensity interval exercise in patients with moderate COPD suggests that intermittent exercise may be superior to continuous exercise among this population. Specifically, this study had 10 patients with COPD perform a continuous exercise session and an intermittent exercise session at an exercise intensity of 70% of peak power output. Participants were encouraged to exercise until the limit of tolerance during both sessions. Sessions were terminated if the participant reached 30 minutes of the continuous protocol and/or 60 minutes of intermittent exercise. Results from this study showed a significantly lower degree of dynamic lung hyperinflation (change in expiratory lung volume) during intermittent exercise compared to continuous exercise (Sabapathy, Kingsley, Schneider, Adams, & Morris, 2004). Similar results were reported in a study of 14 patients with moderate to severe COPD who completed a continuous constant work rate exercise protocol and a HIIE protocol. The continuous protocol involved cycling at 80% of peak work rate and the HIIE protocol consisted of 30 seconds at 70% of peak work rate, based on results from a steep ramp anaerobic test, separated by 90 seconds at 20% of peak work rate, based on results of a cardiopulmonary exercise test. Results indicated that this HIIE protocol was well tolerated and allowed patients to complete nearly double the total work achieved during the constant continuous exercise protocol prior to symptom limitation (Butcher et al., 2013).

HIIE has also been shown to be an effective mode of exercise among patients with CF. Specifically, in a randomized controlled trial 72 patients (age: 7-19 years) with mild to moderate CF were randomly assigned to an exercise group or a control group for 3 years. Patients in the exercise group were asked to participate in aerobic exercise for a minimum of 20 minutes, at a heart rate of approximately 150 beats/min, 3 times per week. At the 3 year follow up a significantly slower rate of decline in pulmonary function was observed in the exercise group (Schneiderman-Walker et al., 2000). Unfortunately, limited research is available on the feasibility of HIIE in patients with CF. Of the research available, it has been suggested that HIIE may be an effective and efficient training regimen among this population. For example, in a case study of a 16-year old female patient with CF a 6-week HIIE exercise intervention was implemented. The HIIE protocol consisted of 30 seconds of high intensity (50-90% of maximum short-time exercise capacity) followed by a 60 second recovery period (25% of maximum short-time exercise capacity). Following the exercise intervention an 18% increase in VO_{2peak} and a 16% increase in work capacity was observed (Hulzebos, Snieder, van der Et, Helders, & Takken, 2011). These results require further investigation before definitive conclusions can be made; however, given the lower toll on the respiratory system required during HIIE, this form of exercise seems promising among patients with pulmonary impairments.

The success of HIIE in clinical populations with pulmonary diseases described above offers a promising rationale for the implementation of HIIE among adults with EIBC. The significant ventilatory impairment associated with COPD and CF is often greater than the impairment observed in individuals with EIBC; therefore, it is likely that HIIE will be feasible and effective within this population as well.

2.5 EXERCISE PSYCHOLOGY

The adverse asthma symptoms commonly experienced during and after exercise participation are of particular concern in terms of promoting exercise adherence among this population. These symptoms may lead to an increase in perceptions of discomfort, particularly breathlessness, thus contributing to a lack of enjoyment. This is of particular interest for adults with EIBC based on research on the exercise-affect-adherence relationship. Specifically, research has shown that affect during exercise can predict future engagement in that activity.[2,3] This decreased affect may help to explain why exercise participation rates are suboptimal among those with EIBC.

As well, research indicates that exercise intensity plays an important role in exercise performance and can influence motivation to perform and continue exercise. Specifically, high intensity activity is typically associated with declines in affective valence (i.e. reduced pleasure) among those with chronic conditions (Ekkekakis & Petruzzello, 1999).This is of particular interest given that MIIE follows the same protocol in terms of work/rest ratio however, at a lower intensity. Therefore, it is possible that interval exercise may be more effective in eliciting positive affect if conducted at a lower intensity; however, no research to date has examined this among those with EIBC. Limited research exists on the affective response to various exercise intensities among those with EIBC. Although affect has been reported to be lower with higher intensity activity; dramatic variability exists in the preference of exercise intensity among individuals (Ekkekakis, 2003). For example, in a study of 29 adult habitual walkers, participants were asked to walk at a self-selected pace. The self-selected walking intensity was 51.5% of VO_{2max}; however, the range was from 35.5 to 79.1% of VO_{2max} (Spelman, Pate, Macera, Ward, 1993). This wide range of exercise intensity preference highlights the importance of individual differences in exercise prescription and requires further investigation in order to determine whether certain subgroups exist in exercise intensity preference among specified populations i.e. those with EIBC.

Conflicting findings of affect during HIIE have been reported in the literature; while some studies have reported lower affect during HIIE as compared to moderate continuous exercise others have reported the opposite (Saanijoki et al., 2015; Oliverira, Slama, Deslandes, Furtado, & Santos, 2013). In a study by Jung and colleagues the affective responses to HIIE and MICE among inactive adults was explored. Results from this study showed that exercise affect was significantly greater during HIIE when compared to MICE (Jung, Bourne, & Little, 2014). The reasons for the observed variability across studies in exercise affect during high intensity activity is not completely understood. However, one possible explanation for a higher exercise affect during HIIE may be partially attributed to the recovery intervals associated with HIIE. For example, these recovery periods may allow for breaks in the cognitive demands of intense exercise, which may be of particular importance given that mental stress increases perceptions of effort and can reduce endurance performance (Marcora, 2009). The recovery periods associated with HIIE may also allow participants to 'catch their breath', which is particularly important for adults with EIBC and may make it cognitively easier to complete interval versus continuous exercise (Kilpatrick et al., 2015). Of note, results from the above mentioned studies are not specific to those with EIBC; therefore, it remains unclear as to whether the affective response to HIIE would be similar among those with EIBC.

Unfortunately, limited research exists on the affective response to exercise among those with EIBC. Of the research available on exercise affect and HIIE it remains unclear as to whether high intensity interval activity would elicit a positive or negative change in affect among those with EIBC. It is possible that although HIIE is composed of high intensity bursts, the recovery periods associated with HIIE may allow for ventilation to recover and may contribute to greater affect among those with EIBC, given that their perceived dyspnea may be lower than that typically experienced during MICE.

2.6 RATIONALE

Intensity and duration are important determinants of the physiological adaptations that occur in response to exercise training (Rees, Taylor, Singh, Coats, & Ebrahim, 2004). As well, intensity and duration play an important role in the psychological responses to exercise, and can predict long term exercise adherence (Ekkekakis & Petruzzello, 1999). Longer duration activities require a substantial time commitment and may exacerbate asthma symptoms by increasing ventilation for prolonged periods (Burton, Stokeks, & Hall, 2004). On the contrary, the duration of the increase in ventilation associated with HIIE is short and followed by intermittent recovery periods, which may offer protective effects of bronchoconstriction in adults with EIBC by reducing the amount of water and heat loss in the lungs. Additionally, these intermittent recovery periods may reduce perceptions of dyspnea during exercise and therefore contribute to greater exercise affect and enjoyment among those with EIBC.

It is clear that regular exercise in adults with asthma elicits a plethora of health benefits such as improved asthma control, improved psychosocial health, and lowers the risk of comorbidities. However, EIBC remains a significant barrier to regular exercise among this population. Therefore, a better understanding of the optimal exercise intensity for adults with EIBC is required.

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CHAPTER 3: SYSTEMATIC REVIEW

TITLE: THE ACUTE RESPONSE TO HIGH INTENSITY OR MAXIMAL INTENSITY EXERCISE IN ADULTS WITH CONFIRMED AIRWAY HYPER-RESPONSIVENESS: A SYSTEMATIC REVIEW.

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3.1 ABSTRACT

Background: High intensity exercise has become a popular form of exercise; however, exercise leads to acute bronchoconstriction among adults with airway hyperresponsiveness (AHR). The purpose of this systematic review was to determine whether an acute bout of high intensity or maximal intensity aerobic exercise would lead to a decline in lung function, adverse events or symptoms in adults with confirmed AHR.

Methods: We performed a systematic search in PubMed and CINAHL in June 2015. Studies were included if they conducted an exercise session without prior use of bronchodilators and if they assessed either post-exercise pulmonary function, signs and symptoms, or adverse events among adults with confirmed AHR.

Results: Twenty-one articles with 348 participants were included. Twenty of the included articles conducted high intensity or maximal intensity exercise (>80% exercise capacity). Following high intensity exercise, the decline in forced expiratory volume in 1 second ranged from 6-27.2%. Treadmill exercise and exercise on a cycle ergometer were among the most common modes of exercise testing. There was vast great variability in exercise protocols, assessing lung function, and diagnostic cut points. Four studies reported on adverse symptoms following exercise.

Conclusion: It appears that high intensity continuous exercise leads to clinically relevant changes in lung function.

3.2 INTRODUCTION

Exercise leads to acute bronchoconstriction in adults with airway hyperresponsiveness (AHR). Approximately 90% of adults with asthma experience exercise-induced bronchoconstriction (EIBC) (Weiler et al., 2007); however, adults without asthma may also experience EIBC and related symptoms as a result of exercise (Parsons et al., 2013). An exercise intensity of 80-90% of age predicted maximum heart rate is typically sufficient for eliciting a positive EIBC response for diagnostic purposes (Anderson et al., 2010); however, it is not clear if a lower intensity would have a similar effect. It is possible that any exercise above the ventilatory threshold would trigger EIBC since high ventilation is the true trigger for EIBC. Research indicates that significant differences can be observed in the decline of forced expiratory volume in 1 second (FEV_1) between exercise at 85% compared to exercise at 95% of maximum heart rate (Carlsen, Engh, & Mork, 2009); but the lowest exercise intensity that could trigger EIBC remains unknown.

Exercise at an intensity of 80% or greater is considered high intensity exercise. There has been a recent growth in popularity of high intensity interval exercise for recreation and athletic training purposes. Considering that an exercise intensity of 85% is used in exercise challenge tests to confirm EIBC, this form of exercise raises important safety concerns for adults with AHR. While high intensity exercise has been shown to be safe in adults with other respiratory conditions such as, chronic obstructive pulmonary disease and cystic fibrosis (Butcher et al., 2013; Hulzebos, Sneider, van der ET, Helders, & Takken, 2011) it is not clear if high intensity exercise would be appropriate in adults with AHR, due to the increase in ventilation and resulting EIBC.

To our knowledge, no systematic review has been conducted with the express purpose of assessing the acute response to high intensity exercise in adults with AHR. Therefore, the purpose of this review was to determine if near maximal (high intensity), maximal or supra maximal aerobic exercise induces asthma symptoms (i.e. decline in lung function, coughing, wheezing) in adults with EIBC. The secondary purpose of this review was to determine if there is an aerobic exercise intensity i.e. a threshold, associated with EIBC.

3.3 METHODS

Registration

The study was registered on June 10, 2015 through PROSPERO International prospective register of systematic reviews (registration number CRD42015023297). All studies included in this review had ethics approval.

Search

The literature search was performed through the following electronic databases: PUBMED and CINAHL. A computerized search for all studies containing the following search terms (last search performed on June 1, 2015): (asthma OR bronchoconstriction) AND (exercise) AND (aerobic).

Eligibility and Study Selection

All titles and abstracts of the computerized search were independently screened by two investigators (CO and SG) for potential relevance. The following studies were excluded: animal studies, studies with participants 18 years or younger, studies that did not confirm AHR through a provocation or medical test, studies that did not with-hold medication prior to exercise, studies that conducted exercise in extreme environmental conditions (with the exception of studies using dry air), reviews, guidelines, letters, commentaries, lectures and addresses, consensus development statements and studies not published in English.

Relevant publications were excluded if published only as an abstract, poster or short communication and if repeated measures of lung function were not obtained at baseline.

Quality Assessment

All studies were independently reviewed by two reviewers to assess quality. Quality was assessed by following a modified quality assessment checklist according to the Scottish Intercollegiate Guidelines Networkd (SIGN) protocol. Studies that did not report use of an objective exercise intensity measure, had an unclear research question, or did not provide sufficient detail on lung function measures (i.e. lung function measures were not taken in accordance with an International guidelines, such as ATS, GINA), were excluded.

Risk of Bias Within and Across Studies

With regards to misclassification bias, all studies included in the review used objectively measured data, thus minimizing the risk of misclassification. Specifically, EIBC was confirmed by the response of FEV_1 to challenge tests, exercise intensity was based on heart rate or oxygen consumption, and the acute response to exercise was monitored with spirometry.

With regards to confounding bias, factors such as temperature and humidity, diet, control or severity levels, and fitness levels are likely to influence the acute response to exercise in this population. While many studies addressed laboratory temperature and humidity, few addressed issues pertaining to diet or fitness levels. Nine studies did report that the participants had "mild, mild-persistent, or mild to moderate" asthma; however, there was some variability in how these categories were established. With regards to our review, data from studies where exercise was performed in non-normal environmental conditions were not included; however, data from studies where exercise was performed outdoors were included.

Selective reporting may be a concern as few studies reported any adverse symptoms or events. Further, there is risk of publication bias, in that studies where no response was observed in response to exercise may not have been published.

Data Collection and Items

A data extraction sheet was developed to ensure consistency in data extraction by two of the investigators. Following extraction, both investigators checked the extracted data. In cases of inconsistency, results were discussed with a third investigator (SD).

The data collection sheet was designed to extract information from each study on the following: 1) participant characteristics (including age, asthma control and fitness levels); 2) type of AHR confirmation test conducted (including protocol details); 3) variables measured (including diagnostic criteria and time intervals for post-exercise lung function measures); 4) symptoms reported (including self-reported coughing, wheezing, shortness of breath and mucus production).

In studies where groups had adults with and without AHR, only data from those with AHR were included. Individual data on pre-post exercise lung function were only available for two studies; however, efforts were made to contact all authors in order to obtain individual data from all included studies. Due to lack of responses and lack of homogeneity of the two studies with individual data, data could not be pooled for meta-analysis.

Summary Measures

The main outcomes for the primary and secondary research question were lung function, adverse events and/or self-reported symptoms. For the primary purpose, only data from high intensity exercise sessions (≥80%) were used; for the secondary research question, only data from submaximal exercise (<80%) were included.

3.4 RESULTS

Study Selection and Characteristics

The search revealed 205 citations, of which 107 potentially relevant articles were identified. Of these, 48 were retrieved for a more detailed evaluation. After the evaluation process, 21 articles on 19 different studies were included (Figure 1). These studies yielded a total sample size of 348 adults with AHR. All studies conducted near-maximal or incremental to maximal intensity exercise sessions; these were mostly exercise challenge tests and thus met our inclusion criteria. One study also conducted submaximal constant load and submaximal interval exercise sessions while breathing dry air at 50% and 40-60% of maximal exercise capacity, respectively (Johnson, Scanlon, & Beck, 1995). There were no studies on supramaximal intensity exercise.

Synthesis of Results

Data were synthesized through qualitative assessment of each study using the following information: 1) participant characteristics 2) lung function response to exercise 3) mode of exercise performed 4) intensity of exercise and 5) criteria for confirmation of

AHR. A summary of the methods and data from each of the 23 studies can be found in Table 1; studies are separated by mode of exercise (a. Treadmill, b. Cycling, c. Outdoor Running).

Population Characteristics

Asthma control or severity was not consistently reported; however, 8 studies reported that participants presented with mild-persistent, mild-moderate or stable asthma (Milanese et al., 2009; Svensson, Nilsson, Bjermer, & Tuffvesson, 2012; VanHaitsma et al., 2010; Garcia-Rio et al., 2006; Mickleborough, Lindley, & Turner, 2007; Pavord et al., 1994; Rossman et al., 2014; Dessanges et al., 1999). Control and severity levels were most commonly determined based on the American Thoracic Society and the Global Initiative for Asthma criteria (Svensson et al., 2012; Garcia-Rio et al., 2006; Rossman et al., 2014; Rubinstein et al., 1988). Additional methods of determining control and severity were based on clinical history (Garcia-Rio et al., 2006), clinical history of medication use/change leading up to the study, history of dyspnea post exercise, and pulmonary parameters (FEV_1 > 80% predicted) (VanHaitsma et al., 2012; Garcia-Rio et al., 2006; Mickleborough et al., 2007; Dessanges et al., 1999). One study based asthma severity on the requirement for inhaled medication only (Pavord et al., 1994).

Training status of participants varied across studies. Specifically, two studies included highly trained/elite athletes (Helenius, Tikkanen, & Haahtela, 1998; Sallaoui et al., 2009) two studies included participants who were moderately trained or recreational athletes (VanHaitsma et al., 2010; Mickleborough et al., 2007) and one study reported that participants were physically active (Evans, Rundell, Beck, Levine, & Baumann, 2005a; Evans, Rundell, Beck, Levine, & Baumann, 2005b; Evans, Rundell, Beck, Levine, & Baumann, 2006).

Lung Function

Post-exercise lung function was assessed at various time points across studies. Among the 19 studies included, 16 different time intervals were used to assess post-exercise lung function. The most common time interval for post-exercise lung function assessment was at minutes 5, 10, 15 and 20 (Milanese et al., 2009; Evans et al., 2005a; Evans et al., 2005b; Evans et al., 2006).

Among the near-maximal and maximal intensity exercise studies (n=18), the decline in FEV_1 ranged from 6–27.2%. Of note, only 2 of these studies reported an average below the clinically relevant threshold of <10% (Svensson et al., 2012; Milanese et al., 2009). Treadmill testing and exercise on a cycle ergometer were the most common modes of exercise. Seven of the 21 studies used a treadmill protocol while participants breathed room air (Svensson et al., 2012; Mickleborough et al., 2007; Rubinstein et al., 1988; Hulks, Mohammed, Jardine, Connell, & Thomson, 1992; Kanazawa, Hirata, & Yoshikawa, 2000; Kanazawa, Hirata, & Yoshikawa, 2002; Reiss, Hill, & Harman, 1997). Six of these studies reported a decline in lung function that ranged from 8-37% (Svensson et al, 2012; Mickleborough et al, 2007; Rubinstein et al., 1988; Hulks et al., 1992; Kanazawa, Hirata, & Yoshikawa, 2002; Reiss, Hill, & Harman, 1997). The remaining study displayed a drop in FEV_1 through a figure; the estimated drop in FEV_1 was 36.6% (Kanazawa, Hirata, & Yoshikawa, 2000). Three studies conducted exercise on a cycle ergometer while participants breathed room air and the decline in lung function following ranged from 6-26.6% (Milanese et al., 2009; Garcia-Rio et al., 2006; Rossman et al., 2014). Outdoor running was used in four studies and decline in FEV_1 following outdoor running ranged from 9.6-28.7% (Helenius et al., 1998; Sallaoui et al., 2009; Brutsche, Britschgi, Dayer, & Tschopp, 1995; Koh & Choi, 2002). Of note, a 6.5% reduction in lung function was defined as "probable EIBC" in one of these studies (Helenius et al., 1998).

Five studies and 7 articles conducted exercise sessions using dry air (Johnson et al., 1995; VanHaitsma et al., 2010; Pavord et al., 1994; Dessanges et al., 1999; Evans et al., 2005a; Evans et al., 2005b; Evans et al., 2006). Of these studies, two conducted exercise on a treadmill and reported an average decline in FEV_1 of $14.3 \pm 3.5\%$ and 13.6% (Garcia-Rio et al., 2006; Pavord et al., 1994). The remaining three studies conducted exercise sessions on a cycle ergometer; the average fall in FEV_1 ranged from 10.1–26.2% (Dessanges et al., 1999; Evans et al., 2005a; Evans et al., 2005b; Evans et al., 2006).

Various cut points were used to determine a positive EIBC response following exercise. A positive response for EIBC ranged from a 7-20% decline in FEV_1. The majority of studies (7/21) utilized a 10% decline in FEV_1 (Johnson et al., 1995; Milanese et al., 2009; Svensson et al., 2012; VanHaitsma et al., 2010; Garcia-Rio et al., 2006; Helenius et al., 1998; Brutsche et al., 1995). The second most common cut point was 20% (Pavord et al., 1994; Rubinstein et al., 1988; Hulks et al., 1991; Kanazawa et al., 2000; Kanazawa et al., 2002; Reiss et al., 1997) followed by 15% (Dessanges et al., 1999; Sallaoui et al., 2009; Koh & Choi, 2002) and 12% (Mickleborough et al., 2007; Rossman et al., 2014). One study used a liberal decline in FEV_1 of 7% following an EVH challenge (Evans et al., 2005a; Evans et al., 2005b; Evans et al., 2006).

Individual data were not reported in the majority of studies; therefore, an accurate average decline in post-exercise lung function could not be determined. Individual data were reported in one study at ambient temperatures. They reported a median fall in FEV_1 of 29.7% (range of 19.9-62.3%) (Reis et al., 1997). A second study reported individual data; however this study conducted the exercise session while participants were breathing dry air. The average decline in lung function was 26.2 ± 13.1 (Dessanges et al., 1999).

In the one study that included submaximal exercise, ventilatory capacity was estimated using various techniques and the change in ventilatory capacity was described during incremental, constant-load, and interval exercise. EIBC was confirmed by a 10% drop in lung function following at least 1 exercise session. Participants warmed up for 3 mins at 20W; the work rate increased to 50% of the participants maximal exercise capacity. Every 6 minutes a maximal end flow volume maneuver was performed and exercise was continued for 36 mins at a constant rate. On separate days, interval exercise with a 3 min warm up at 20 W and changing work rate (60% and 40% of participants maximum capacity for 6 minutes each, repeated 3 times) was performed. It was concluded that continuous aerobic exercise for 36 minutes in most patients with asthma does not have a negative impact on airway function (Johnson et al., 1995).

Adverse Events/ Symptoms

Of the 19 studies included, few studies reported adverse events/symptoms. One study reported that of the 23 participants that completed the study, five reported 10 adverse events (Dessanges et al., 1999); however, only two adverse events were reported in the paper; these were worsening of allergic rhinitis (n=1) and pharyngitis (n=1). One study reported that many participants complained of symptoms during and after exercise; however, no details were given on these symptoms (Mickleborough et al., 2007). One study reported that EIBC occurred in three participants following at least 20 minutes of exercise at approximately 55% of maximal workload or until exhaustion, whichever came first (Milanese et al., 2009). One study reported that all participants reported symptoms that were consistent with EIBC during/after exercise; however, no details on these symptoms were given (Evans et al., 2006).

3.5 DISCUSSION

The goal of this systematic review was to synthesize information on the acute response to near-maximal and maximal intensity exercise as well as to identify an exercise intensity threshold that triggers EIBC in adults with AHR. The primary finding of this review is that near-maximal and/or maximal intensity continuous exercise appears to induce clinically relevant changes in lung function in most, but not all adults with AHR. The secondary finding is that the mode of exercise does not appear to impact the effect of near-maximal or maximal intensity exercise in this population. These findings have important implications for future research. Specifically, future research should be conducted in order to better understand the impact of various exercise intensities on EIBC and seek to determine whether an exercise threshold that triggers EIBC exists.

Our finding that continuous exercise over 80% of maximal capacity for 6 to 10 minutes leads to a decline in FEV_1 was not surprising. Guidelines indicate that high intensity continuous exercise, particularly when inhaling dry-air, can be used to confirm EIBC (Parsons et al., 2013). However, in many of the studies reviewed, this exercise was progressive i.e. the entire time was not spent at near-maximal intensity or high ventilation. In fact, the time spent at near-maximal intensity continuous exercise was closer to 2-3 minutes in duration. This is important because the recent popularity of high intensity interval exercise has encouraged the general population to improve their health and fitness with high intensity interval exercise. While there is no standard protocol, the bulk of the research has used one minute intervals at high intensity and low intensity

(Little, Safdar, Wilkin, Tarnopolsky, & Gibala, 2010). It is not clear from the data presented in this review whether this interval timing would be safe for those with AHR.

Another interesting finding was that not all adults with AHR had a clinically relevant decline in lung function. Such individual differences are expected (Goodman & Hays, 2008); however, the factors related to these differences are important to understand. Factors such as asthma control levels, cardiorespiratory fitness or long acting medication use may be confounders. Unfortunately, most papers did not report on this information, making it difficult to make any inferences.

The finding that lung function declined regardless of mode of exercise is consistent with previous research. While swimming has been shown to be particularly good for preventing EIBC due to the warm-humid air, both cycling and running produce significantly greater changes in lung function among those with AHR (Goodman & Hays, 2008). Further, during indoor exercise, cycling and running have been shown to produce similar responses (Kallings, Emtner, & Backlund, 1999). Of interest, the outdoor running studies had similar ranges of lung function decline. Due to the higher number of allergens and variable climatic conditions, changes in lung function in these studies was expected to be higher.

We were unable to draw conclusions on adverse events and symptoms due to lack of reporting. Given the importance of perceived breathlessness in this population, future studies should consider self-report during exercise. Further, due to the variability in studies, it is difficult to know whether there is an exercise intensity below 80% that does not trigger bronchoconstriction. Further, adverse events should be reported to determine the safety of such exercise. As well, participant characteristics varied widely. For example, participants included were athletes, recreationally active, and soldiers and some studies did not provide detail on participants; thus, generalizability of these results are limited.

There appears to be a large amount of variability in exercise testing among adults with AHR. Specifically, variability exists surrounding the timing of lung function measures, diagnostic cut points, exercise intensity/protocol and environmental conditions.

These inconsistencies illustrate the need for standardization in exercise testing among this population.

In conclusion, using data from 21 studies, we found that continuous exercise above 80% of age predicted maximum heart rate with no prior short acting medication, leads to a clinically relevant decline in lung function in most, but not all adults with AHR. Future research is needed to better understand the response to high intensity interval exercise and to establish an exercise intensity threshold below which adults with AHR can safely exercise.

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Table 1. Study Characteristics.

Citation	Sample Size and Sample Characteristics	Cut Point (n=# meeting this criteria)	Exercise Protocol	Average % Decline in FEV_1 Post Exercise
Treadmill				
Svensson et al., 2012	Participants with mild asthma n= 20 (males n=11; females n=9) Age: 22 (21-25.3)+	10% drop in FEV_1 post exercise (n=7)	No warmup, exercise session was divided into 3 phases: 1) First 2 minutes: speed and level of slope were set to increase heart rate to approximately 90% of calculated maximum capacity 2) 4 mins: Speed and level of slope adjusted to keep the participants heart rate steady 3) Last 2 mins: speed and level of slope were increased to push the heart rate above the level of the previous phases and induce maximal exertion.	8 (5-13)+

VanHaitsma et al., 2010	Moderately trained recreational athletes with physician diagnosed asthma and a history of exercise induced bronchoconstriction n=13 Age: 20.9 (0.7)++	10% drop in FEV_1 post exercise screening (n=13)	Participants ran on a treadmill until 85% of age predicted maximal heart rate and until ventilation exceeded 40-60% of predicted MVV. Following 3 minutes of steady state the grade of the treadmill was increased 1% per minute until volitional exhaustion. *Data presented are based on results from the pre-screening exercise test and the placebo (0mg/kg caffeine, placebo-albuterol)*	^18.4 (7.2) ++ 14.3 (3.5)++ (n=10)
Mickleborough et al., 2007	Moderately trained recreational athletes with physician diagnosed asthma n=8 Age: 19.5 (1.2)++	10% drop in FEV_1 post exercise (n=8)	Participants ran on a treadmill (no warm-up) until 85-90% predicted maximal heart rate was reached. Once target heart rate was reached the participant entered steady state exercise for another 8 minutes.	18.3 (4.0)++

Hulks et al., 1991	Atopic men with asthma. n=8 Age: 32.1 (9.7)++	20% - from a previous submaximal treadmill test (n=8)	Following a submaximal exercise test to confirm exercise induced bronchoconstriction (data not provided) participants returned to complete a treadmill test using the Bruce protocol.	27.1 (4.8) ++
Kanazawa et al., 2000	Adults with asthma. n=18 Age: 27.6 (2.6)++	20% drop in FEV_1 post exercise (n=9)	Six minutes on treadmill at 90% predicted heart rate maximum.	*36.6 (20-65) +
Kanazawa et al., 2002	Non-smoking adults with asthma. n= 23 Age: 34.8 (7.8)++	20% drop in FEV_1 post exercise (n not reported)	Six minutes on the treadmill at 90% heart rate of the maximum predicted for their age.	24 (13.3)++
Reiss et al., 1997	Males with exercise induced bronchoconstriction. n=14 Age:18-46+	20% drop in FEV_1 post exercise from two separate visits (n=13)	Participants completed 2 pre-screening exercise sessions on the treadmill for 6 minutes. Gradient and speed of the treadmill were adjusted to achieve a workload of	29.7 (19.9-62.3)+

			more than 80% of participants' age-predicted maximum heart rate. *Data presented are an average of the 2 pre-screening exercise sessions.*	
Rubinstein et al., 1980	Non-smoking adults with asthma. n=14 Age: 30 (7)++	20% drop in FEV_1 post exercise (n=14; males n=10; females n=4)	Participants exercised for 6 minutes. Speed and grade were adjusted such that participants achieved at least 80% of their predicted maximal heart rate.	37 (15)++
Pavord et al., 1994	Males with mild asthma. n=13 Age: 18-45+	15% drop in FEV_1 post exercise (n=13)	Exercise lasted for 7 minutes in room temperature environment breathing dry air on a treadmill. Speed and grade were set at a level to maintain a heart rate of 80% of the predicted maximum for each participant.	13.6 (2.7) +++
Cycling				
Evans et al., 2005	Physically active non-smoking individuals with	7% drop in FEV_1 post EVH	Six minutes of cycling on a stationary bicycle at the highest sustainable intensity for the	9.1

Evans et al., 2005 Evans et al., 2006	probable exercise induced bronchoconstriction. n=22 Age: 25.2 (8.4)++	N=22 (males n=10, females n=12)	duration of the exercise. Participants were verbally instructed to give maximal effort at all times.	
Milanese et al., 2009	Adults with mild to moderate asthma. n=18. Incremental exercise: n=10 Age: 27 (5) ++ Constant Load: n=8 Age: 35 (12) ++	10% drop in FEV_1 post exercise (n not reported)	Incremental to maximal exercise test: Workload was increased by 25W every 2 mins with the participants cycling at 60 rpm until exhaustion. Constant Load: Began at a workload that would equal approximately 55% of maximal workload. Approximately 60 rpm for at least 20 minutes or until exhaustion, whichever came first. *Data presented is based on participants who received the placebo*	Incremental Placebo: 6 (10) ++ Constant load placebo: 26 (22) ++
	Non-smoking, steroid naïve,	10% drop in FEV_1 post exercise	Work intensity was selected for each individual participants to	19.5 (2.5) +++

Garcia-Rio et al., 2006	atopic adults with mild stable asthma. n=25 Age: 33 (18-65)[+]	(n=11) Age: 32 (2) [++]	achieve a minute ventilation between 40 and 60% of his/her predicted maximal voluntary ventilation (35 x FEV_1 predicted) during 6 minutes.	
Rossman et al., 2014	Adults with mild asthma. n=8 Age: 30.4 (8.4)[++]	12% drop in FEV_1 post exercise (n=8; male n=5; female n=3)	Participants completed an incremental to maximal exercise test on a cycle ergometer.	26.6 (15.3) [++]
Dessanges et al., 1999	Non-smoking adults with stable asthma. n=24 Age: 18-45[+]	15% drop in FEV_1 post exercise (n=22) 10% drop in FEV_1 post exercise (n=2)	Exercise on a cycle ergometer while inspiring dry air at room temperature. The workload was rapidly increased over 2 to 3 mins until 80% of age predicted maximum heart rate was reached. Exercise was continued for an additional 6 minutes.	26.2 (13.1) [++]
Outdoor				
Brutsche et al.,	Soldiers from a military school	10% drop in FEV_1 post exercise	Free running for 8 minutes. Participants had to achieve over	*12.0 (3.5) [++]

1995	n=289 Age: 20	(n=17)	80% heart rate maximum by the end of the session.	
Helenius et al., 1998	Elite runners. n=58 Age: 24 (5.6)++	Positive EIB: 10% drop in FEV_1 post exercise (n=5) Probable EIB: >6.5% drop in FEV_1 post exercise (n=15)	No warm up. Participants completed a 2000 meter run on an outdoor track during the winter and pollen season. During the first 500m, athletes accelerated raising heart rate to 85% of their personal maximum (calculated by 205 – 0.5 x age).	*Positive EIB: 14.3 (5.7) ++ Probable EIB: 9.6 (4.7) ++
Koh and Choi., 2002	Men with previously diagnosed asthma. n=69 Winter: n=25; age: 20.1 (1.5)	15% drop in FEV_1 post exercise (n=51)	Free running for 6 minutes in either the winter, spring/autumn or summer season. During the first 2-3 mins, participant s accelerated, raising their heart rate to 85% of maximum. They maintained that velocity for the next 4 mins.	28.7

	Spring/autumn: n=22; age: 20.3 (1.7) Summer: n=22; age: 19.7 (1.4)			
Sallaoui et al., 2009	Elite athletes (mixed endurance and power). n=326 Age: 20.8 (2.69)++	15% drop in FEV_1 post exercise (n=32) Age: 21.13 (2.64) ++	Athletes ran for 8 minutes at 80–85% of the estimated maximum heart rate.	16.8 (2.30)++

FEV_1, forced expiratory volume in 1 second;

*, Estimated from figure

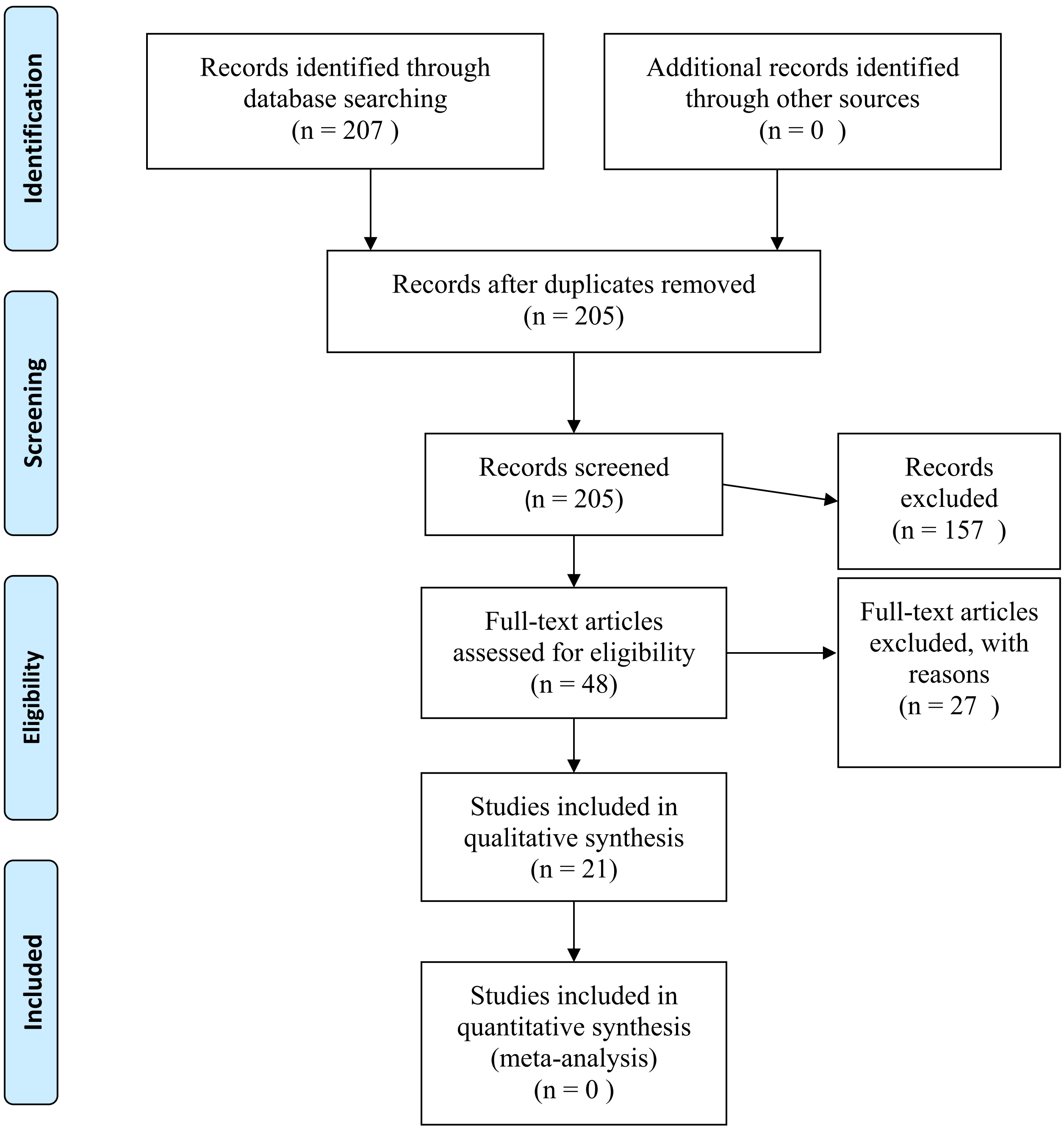
+, Range

++, Standard Deviation

+++, Standard Error

^, Data from exercise pre-screening test

Figure 1. PRISMA Flow Diagram



CHAPTER 4: EXTENDED METHODS

4.1 METHODOLOGY

Study Design: Randomized cross-over design of three experimental protocols.

Participants: Adults with physician-diagnosed asthma aged 18-44 years were recruited for this study. The upper age limit of 44 years was to minimize inclusion of participants who may have chronic obstructive pulmonary disorder (COPD). Inclusion was further limited to those who had a current prescription for short acting beta-agonist medication, those with a positive response to the eucapnic voluntary hyperpnea (EVH) challenge (described below), and to those who were meeting the current minimum Canadian physical activity guidelines of 150 minutes of moderate to vigorous aerobic activity per week. This was to ensure that participants were not accustomed to high intensity exercise associated with high ventilation, but were able to complete the exercise sessions at the intensities required. Participants were excluded if they had a current injury or were unable to exercise on a cycle ergometer.

Recruitment: Recruitment was done through student and faculty wide email, through the distribution of posters, classroom announcements, and through word of mouth. Posters were distributed around the UOIT and Durham College campus in order to recruit both students and faculty. Seven participants were recruited through the use of posters. Permission was sought from course instructors to make classroom announcements in undergraduate courses. Three participants were recruited through classroom announcements and the remaining three participants were recruited through word of mouth.

4.2 MATERIALS

Baseline Questionnaires:

- Eligibility Questionnaire– This questionnaire included questions on the inclusion/exclusion criteria (Appendix B1).
- Physical Activity Readiness Questionnaire Plus (PAR-Q+) – The PAR-Q+ is a 4-page form that asks questions on potential risks associated with exercise. It was

used as a pre-screening tool to ensure all participants were cleared to exercise (Appendix B2).

- Demographic Questionnaire – This questionnaire was used to obtain information on basic demographics such as age, sex, physical activity levels, and years with diagnosed asthma (Appendix B3).
- The Asthma Control Questionnaire – The Asthma Control questionnaire was developed and validated to measure asthma control in adults (Juniper, O'Byrne, Guyatt, Feme, & King, 1999). The questionnaire is scored on a 7-point scale with scores ranging from 0 (no impairment) to 6 (maximum impairment). Participants were asked to complete the questionnaire before their first exercise session (Appendix B7).

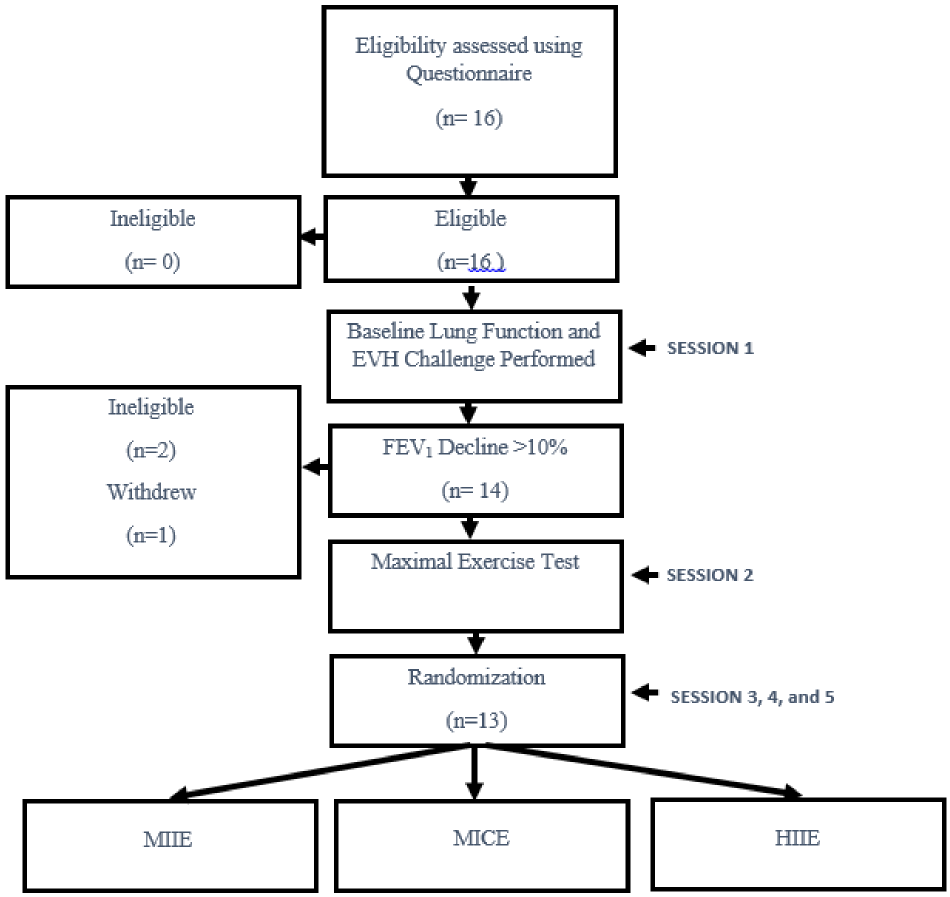
Tools:

The following tools were used during the laboratory visits:

- Spirometer (Vitalograph, United Kingdom): Lung function measures of FEV_1 and FVC were obtained using a handheld spirometer in accordance with the American Thoracic Society/European Respiratory Society standardized protocols (Miller et al., 2005).
- EVH: The EVH challenge reproduces EIBC by hyperventilation of dry gas containing 5% CO_2, 21% O_2 and balanced N_2. The EVH challenge is high in sensitivity and is recommended by the International Olympic Committee Medical Commission IOC-MC (Anderson, 2001) as a reliable tool for screening EIBC.
- Borg Scale of Perceived Exertion (RPE): The Borg scale (6-20) for perceived exertion was used to monitor participant's subjective exertion throughout exercise. RPE was recorded every minute during exercise (Appendix B4).
- Modified Borg Scale for Perceived Dyspnea (RPD): The RPD scale is a tool used to assess feelings of breathlessness in individuals with asthma. RPD was recorded every minute during exercise (Appendix B5).
- One Item Feelings Scale (FS) – The one item FS is a reliable tool to measure in-task exercise affect (Hardy & Rejeski, 1989) (Appendix B7).

- Physical Activity Enjoyment Scale (PACES): This 18-item measure is scored on a 7-point bipolar scale that measures enjoyment of physical activity (Appendix B8).
- Late Phase Asthma Questionnaire – Participants were sent home with the late phase asthma questionnaire to assess coughing, difficulty breathing, and wheezing 24 and 48 hours after exercise. This questionnaire was used to assess any late phase asthmatic responses in participants (Appendix B9).

Overview of Laboratory Visits and Procedures

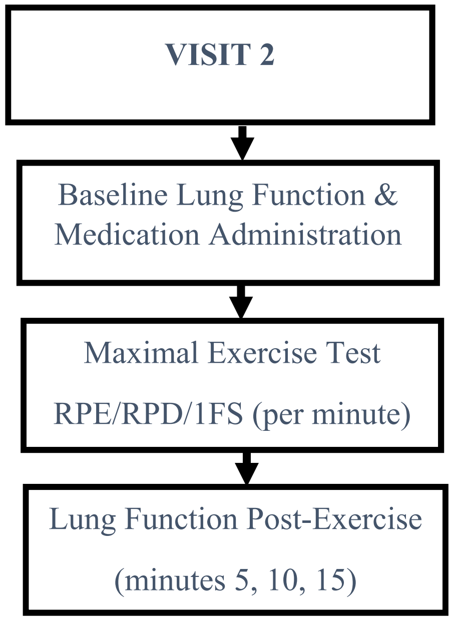


EVH and Familiarization:

- Participants were given the following instructions to follow prior to their laboratory visit: 1) refrain from consuming caffeinated beverages at least 2 hours prior, 2) refrain from consuming a heavy meal at least 2 hours prior, 3) refrain from heavy exercise at least 4 hours prior, 4) refrain from taking any long acting asthma medications at least 48 hours prior to testing and refrain from taking any short acting medication at least 8 hours prior to testing (Anderson, 2001). The latter is to ensure the EVH is able to detect a positive response.

- Upon arrival to the laboratory, participants were asked to complete an exercise pre-screening document and read and sign an informed consent document outlining all procedures, benefits, and risks of participation in the study (Appendix A1).
- Height and weight were measured using a standardized scale (Detecto, Webb City MO, USA) and waist circumference was measured using a tape measure.
- Participants then completed baseline lung function tests, the EVH challenge (protocol below) and follow-up lung function tests.
    - Protocol: The EVH single stage protocol requires hyperventilation for six minutes at a target ventilation rate equivalent to 30 × FEV_1 (litres corrected to body temperature, pressure, and fully saturated (BTPS)) measured immediately before the test. This is only a target ventilation rate. Most asthmatics need only breathe at 21 × FEV_1 to have an abnormal response. However, in order to ensure participants reach a minimum ventilation rate of 21 x $FEV_{1,}$ a target ventilation rate range was determined at 25-30 x FEV_1. Expired ventilation was measured, corrected for time (Anderson et al, 2001).
    - A decline in FEV_1 of 10% or greater is indicative of EIBC (Hurwitz et al, 1995). The percentage decrease in FEV_1 is calculated as follows:
        - 100 x (FEV_1 (before test) – lowest value for FEV_1 (20 minutes after the test) / FEV_1 before test.
- If the participant had a negative response i.e. did not have EIBC as per the EVH challenge, the participant was excluded from the study. If the participant had a positive EVH response, they were scheduled for the maximal exercise testing session and were familiarized with the cycle ergometer, mouthpiece, headset, and nose clip that were used for the maximal exercise testing session.
- Participants were given a demographic questionnaire, an asthma control questionnaire, and a late phase asthma symptom questionnaire upon their departure from the laboratory. They were instructed to complete and return all questionnaires at their next visit. Participants were instructed to complete the late phase asthma questionnaire 24 and 48 hours post-session.

Visit 2

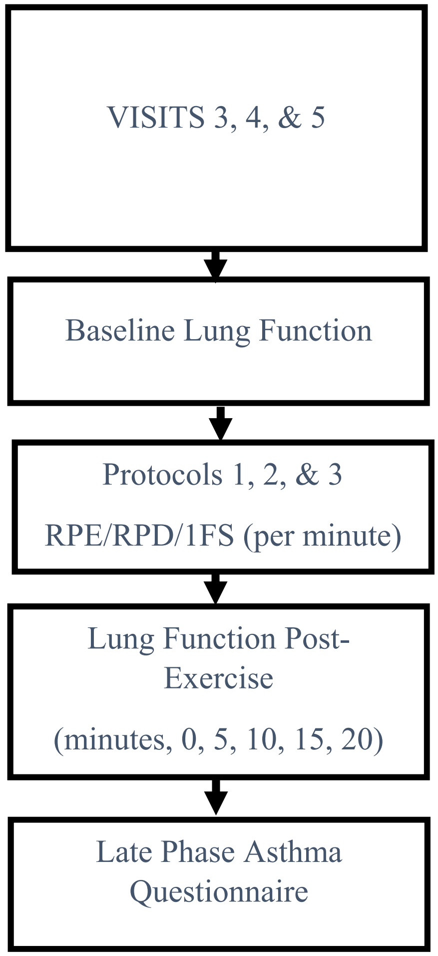


Maximal Exercise Test:

- Participants were given the following instructions to follow prior to their laboratory visit: 1) refrain from consuming caffeinated beverages at least 2 hours prior, 2) refrain from consuming a heavy meal at least 2 hours prior, 3) refrain from heavy exercise 48 hours prior, 4) bring current rescue medication to the laboratory session.
- Resting heart rate was assessed using a Polar heart rate monitor. Blood pressure was assessed using a blood pressure cuff (WelchAllyn, Germany) and lung function was assessed using a handheld spirometer.
- Participants were then be asked to take their rescue medication to prevent EIBC from disrupting the maximal exercise test. Lung function was measured 15 minutes after medication use.

- The cycle ergometer was adjusted to fit each participant prior to exercise testing. Participants were fitted with a head set and mouthpiece. Expired CO_2 and O_2 was collected breath-by-breath through a pneumotachograph and analyzed using an automated gas collection system (Parvo Medics, 2400 USA).
- Exercise Testing Protocol: Participants warmed up at an intensity of 20Watts (W) at a minimum rpm of 50 for five minutes. An incremental to maximal protocol was used. Exercise testing began at 20W and increased by 20W per minute at an rpm of 70-80 until maximal exercise.
- Maximal Oxygen Consumption (VO_{2max}) was be determined by taking the highest value of VO_2 achieved during a 30 second collection period. Upon completion of the exercise test, the head-set was removed and participants entered into a cool down phase at an intensity of 25Watts for five minutes.
- Lung function was be measured again at 0, 5, 10, 15 and 20 minutes post-exercise (Anderson, 2001). Participants were asked to take their medication if lung function had not returned to normal following 15 minutes post-exercise.
- Following completion of the maximal exercise test peak power output was used for calculation of subsequent exercise sessions. Specifically, 10%, 65%, and 90% of peak power output were calculated to determine intensities for the subsequent tests.
- The order of exercise sessions were randomized using an online randomization software (GraphPad software).

Visit 3, 4 and 5



Exercise Sessions:

- Participants were given the following instructions to follow prior to their laboratory visits: 1) refrain from consuming caffeinated beverages at least 2 hours prior 2) refrain from consuming a heavy meal at least 2 hours prior 3) refrain from heavy exercise 48 hours prior, 4) refrain from taking medication up to 8 hours prior to testing and 5) bring current rescue medication to the laboratory.
- Resting heart rate, blood pressure and lung function was assessed.
- The cycle ergometer was then adjusted to fit each participant prior to testing.
- Participants warmed up for 5 minutes at 20 Watts at a minimum rpm of 50 and completed a 5-minute active recovery at 20 Watts following each exercise

session.

- Exercise Protocols:
    - 1) A moderate intensity continuous exercise protocol at 65% of peak power output for 20 minutes
    - 2) A moderate intensity interval protocol at 65% peak power output for 1 minute followed by 10% peak power output for 1 minute, 10 times
    - 3) A high intensity interval protocol at 90% peak power output for 1 minute followed by 10% peak power output for 1 minute, 10 times.

- Heart rate, RPE, RDE, and the FS were recorded every minute during each exercise protocol.
- Lung function was measured again at 0, 5, 10, 15 and 20 minutes post-exercise. (Anderson et al, 2001)
- Participants were asked to complete the late phase asthma questionnaire at 24 and 48 hours post-exercise.
- All exercise sessions took place a minimum of 72 hours apart, in order to prevent a training effect and to ensure lung function is not impaired.

Statistical Analysis

A one-way analysis of variance with the LSD correction applied was used to determine differences across the exercise protocols. A decline in FEV_1 of $10 \geq 10\%$ was considered clinically significant. A chi-square was used to determine differences in asthma symptoms among exercise protocols. A repeated measures two way analysis of variance with pairwise comparisons was used to determine differences within and between exercise protocols for affect, RPE, and RPD. Paired samples t-tests were used to compare the PACES scores between exercise protocols. All statistics were done in SPSS and statistical significance was declared at $p<0.05$.

Sample Size

It was determined that a sample size of 13 would be required (Faul & Erdfelder, 1992); however, in order to account for potential dropout a total of 15 participants were recruited.

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CHAPTER 5: MANUSCRIPT 1

TITLE: THE ACUTE RESPONSE TO INTERVAL AND CONTINUOUS EXERCISE IN ADULTS WITH CONFIRMED AIRWAY HYPER-RESPONSIVENESS.

Submitted to the Journal of Science and Medicine in Sport.

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5.1 ABSTRACT

INTRODUCTION: Exercise induced bronchoconstriction (EIBC) occurs as a result of airway cooling and drying in adults with airway hyperresponsiveness (AHR). Continuous exercise has been shown to lead to a significant decline in lung function and an increase in asthma related symptoms. Interval exercise may allow time for ventilation to recover and thus prevent EIBC. PURPOSE: To determine changes in lung function and reporting of asthma symptoms in response to an acute bout of high intensity interval exercise (HIIE), moderate intensity interval exercise (MIIE), and moderate intensity continuous exercise (MICE) in adults with AHR. METHODS: Participants completed five laboratory sessions: 1) eucapnic voluntary hyperpnea challenge 2) maximal exercise test to determine peak power output (PPO) and, 3-5) high intensity interval exercise (HIIE) (90% PPO for 1 minute followed by 10% PPO for 1 minute, repeated 10 times), moderate intensity interval exercise (MIIE) (65% PPO for 1 minute followed by 10% PPO for 1 minute, repeated 10 times) and moderate intensity continuous exercise (MICE) (65% PPO for 20 minutes). Lung function was assessed pre and post-exercise while late phase symptoms were reported using a log. RESULTS: Thirteen participants (age: 21.1 ± 2.7 years) with mild/moderate asthma completed all protocols. Lung function was significantly lower following the MICE (-14.8% ± 12.2) protocol compared to the HIIE (-7.1% ± 8.3) and MIIE (-4.5% ± 3.3). Participants reported a higher number and greater severity of asthma symptoms following the MICE. CONCLUSION: It appears that MICE is associated with the greatest decline in post-exercise FEV_1 as well as the most late phase symptoms among those with AHR. Interval exercise may be better tolerated than continuous exercise among those with AHR.

Key Words: Bronchoconstriction, exercise-induced asthma, pulmonary function, asthma, interval exercise.

5.2 INTRODUCTION

Airway hyperresponsiveness (AHR), which can be defined as an increased sensitivity of the airways, is a characteristic feature of asthma (O'Byrne & Inman, 2003). Exercise is a trigger for acute bronchoconstriction in adults with AHR and approximately 90% of adults with AHR experience exercise-induced bronchoconstriction (EIBC) (Weiler et al., 2007).

EIBC is thought to occur due to an increase in evaporative water and heat loss from the airways as a result of the increase in ventilation associated with exercise. This increase in ventilation is sustained over an extended period of time during continuous aerobic exercise. As such, an exercise challenge can be used to confirm EIBC (Parsons et al., 2012; Ali, 2011). The high intensity continuous nature of the exercise session, coupled with breathing of dry air, leads to a decline in lung function of 15-20% or more in individuals with AHR. Several studies that have conducted such challenges without prior bronchodilator use (with and without dry air breathing) have reported clinically relevant changes in lung function post-exercise, regardless of the mode of exercise (Kallings, Emtner, & Backlund, 1999; Mickleborough, Lindley, & Turner, 2007; Milanese et al., 2009; Svensson, Nilsson, Bjermer, & Tuffvesson, 2012). Importantly, the high intensity component of these sessions only lasted between 2-3 minutes while the initial 3-5 minutes were of moderate intensity due to the incremental nature of the exercise protocols.

This raises important concerns for the recent trend of high intensity interval exercise (HIIE) in adults with AHR. HIIE includes brief bouts of high intensity exercise at 90-100% of maximal exercise followed by intermittent recovery periods. This intermittent recovery may allow for ventilation to recover and thus reduce the amount of water and heat loss from the airways. A systematic review conducted by Stickland and colleagues (2011) assessed a variety of exercise warm-up protocols to determine whether they would lead to a refractory period wherein individuals with AHR did not experience EIBC in a subsequent exercise session. They found that a HIIE warm-up attenuated the lung function response to subsequent vigorous exercise (Stickland, Rowe, Spooner, Vandermeer, & Dryden, 2011). However, HIIE has not been studied as an exercise prescription option outside of the context of warm-up i.e. the bouts used for warm-up in these studies reviewed were short (6 minutes), intensities varied from 98% of heart rate (HR) max in a study by Reiff and colleagues (1989) and an absolute HR of 180bpm in another study (Schnall & Landau, 1980).

Research indicates that regular exercise can lead to improvements in asthma symptoms, asthma control, and health related quality of life (Dogra, Kuk, Baker, & Jamnik, 2011; Meyer, Gunther, Volmer, Taube, & Baumann, 2015). Unfortunately, physical activity levels among adults remains suboptimal (Colley et al., 2011); particularly among those with asthma (Ford et al., 2004). HIIE may be a time-efficient and enjoyable way for adults prone to EIBC to safely exercise. However, the acute response to interval exercise lasting 20 minutes has not been studied among those with AHR. Further, comparisons are needed to understand whether it is the intensity or continuous versus interval nature of exercise that is relevant to exercise prescription in this population. Therefore, the primary purpose of this study was to assess the acute response to a single session of HIIE, moderate intensity interval exercise (MIIE), and moderate intensity continuous exercise (MICE) in adults with confirmed AHR. We hypothesized that MIIE would be associated with the least asthmogenic response, followed by HIIE.

5.3 METHODS

Study Design and Participants

A randomized cross-over study design was used. Inclusion was limited to adults aged 18-44 years with a current prescription for rescue medication (i.e. short acting bronchodilator) and to those who were accumulating at least 150 minutes of moderate to vigorous intensity physical activity per week. Those who were considered highly trained i.e. varsity athlete or those engaging in >300 minutes of moderate to vigorous intensity physical activity per week, were excluded. This was to ensure that participants were not accustomed to high intensity exercise. Further, AHR was confirmed by a drop in forced expiratory volume in 1 second (FEV_1) of 10% or higher following a eucapnic voluntary hyperventilation (EVH) challenge (described below). All participants completed a screening questionnaire to ensure they were at minimal risk for exercise participation; no participant reported any additional chronic conditions (Canadian Society of Exercise

Physiology, 2013). All participants provided written informed consent prior to laboratory testing and all procedures were approved by the Research Ethics Board of the University of Ontario Institute of Technology.

Procedures

Interested participants completed an eligibility questionnaire and attended one laboratory session to confirm AHR using the eucapnic voluntary hyperventilation challenge. Following a positive AHR response (≥ 10% decline in FEV_1) participants were asked to return to the laboratory on four separate occasions, separated by a minimum of 72 hours. Those participants who did not have a positive AHR response were excluded from the study. Figure 1 displays the eligibility determination and order of laboratory visits. Resting heart rate and blood pressure measurements were taken upon arrival to the laboratory after the participant had rested for a minimum of five minutes prior to each session. Prior to each exercise session, participants were asked to refrain from consuming a heavy meal and caffeinated beverages at least 2 hours. Additionally, participants were instructed to refrain from heavy exercise at least 24 hours prior to each exercise session.

Measurements

Participants were asked to complete a demographic questionnaire and an asthma control questionnaire (ACQ) during their first visit to the laboratory. The latter has been shown to have strong evaluative and discriminative properties and can be used to measure asthma control with confidence (Juniper, O'Byrne, Guyatt, Ferrie, & King, 1999). During each laboratory session, height and weight were measured on a medical scale (Detecto, Webb City MO, USA) and lung function was assessed using a handheld spirometer (Vitalograph, United Kingdom). All lung function measurements were taken in accordance with the American Thoracic Society Guidelines (Parsons et al., 2013). All exercise sessions were conducted using a cycle ergometer (Monark, Ergomedic 894 E). A metabolic cart (Parvo Medics 2400, USA) was used during the maximal exercise test.
Eucapnic Voluntary Hyperventilation (EVH) Challenge: Participants completed three repeatable lung function measures and the highest FEV_1 value obtained was used to determine the target ventilation range for the EVH challenge. Participants completed a single stage six minute challenge at a target ventilation range between 25-30x FEV_1 to confirm AHR. Participants were seated comfortably and inhaled room temperature dry air

composed of 5% CO_2, 21% O_2, and the balance N_2, through a two way valve while wearing a nose clip. Following the challenge, lung function was re-assessed in duplicate and the highest value obtained was recorded at 5, 10, 15, and 20 minutes post-challenge. A decline in FEV_1 of 10% or greater was considered a positive AHR response, calculated as follows:

$$\% \text{ Fall in } FEV_1 = 100\ [FEV_1 \text{ pre-challenge} - FEV_1 \text{ post-challenge}] / FEV_1 \text{ pre-challenge}$$

Familiarization: Participants with a positive response to the EVH challenge were then familiarized with the headset, mouth piece, cycle ergometer, and heart rate monitor used for the subsequent laboratory visits. They were asked to exercise at 20 Watts (W) for one minute, the workload was then increased by 20W every minute for three minutes to ensure participants were familiarized with the step-wise increase of the protocol.

Maximal Exercise Test: Upon arrival to the laboratory, participants completed spirometry. Participants were instructed to take their short-acting medication prior to exercise in order to ensure they were not limited by asthma symptoms during the exercise test and to avoid an unnecessary decline in lung function post-exercise. Lung function was re-assessed 15 minutes post-medication administration. Participants were then fitted with a heart rate monitor, head-set, mouthpiece and the cycle ergometer was adjusted accordingly. Participants began a warm-up at 20 W for 5 minutes. Exercise testing began at 20W and increased by 20W per minute at 70-80 revolutions per minute (rpm) until volitional exhaustion. Participants then moved into an active cool-down. Peak power output (PPO) was determined based on results from the maximal exercise test. Ventilatory threshold (VT) was determined using three methods: 1) the disproportional increase in V_E vs VO_2, 2) by the disproportional increase in V_E vs VCO_2 according to Wasserman *et al*. (Wasserman, Whipp, Koyl, & Beaver, 1973), 3) by using the V-slope method as described by Beaver *et al*. (Beaver, Wasserman, & Whipp, 1986). Participants then completed the three exercise sessions separated by a minimum of 72 hours in random order.

Exercise Protocols: Prior to each laboratory visit, participants were instructed to refrain from taking their short-acting medication at least 8 hours prior to testing. Participants were permitted to continue taking their long acting steroid medication. Participants were fitted with a heart rate monitor and the cycle ergometer was adjusted for each participant. Participants were given a 5 minute warm up prior to each exercise session at 20 W and 70-80 rpm. Exercise sessions were: 1) HIIE (90% PPO for 1 minute, 10% PPO for 1 minute, repeated 10 times), 2) MICE (65% PPO) for 20 minutes, 3) MIIE (65% PPO for 1 minute, 10% PPO for 1 minute repeated 10 times). Participants were instructed to cycle at 70-80 rpm throughout the entire session. Heart rate was recorded at the end of each minute. Lung function was re-assessed immediately post-exercise and at 5, 10, 15, and 20 minutes post-exercise. Participants were sent home with a late phase asthma symptom log to be completed at 24 and 48 hours after the session to determine if there were any late phase symptoms.

Statistical Analyses

Means and standard deviations were used to describe the sample. A one-way analysis of variance with the LSD correction applied was used to determine differences across the three exercise protocols. A change in FEV_1 of $\geq$ 10% was considered clinically significant. A chi-square was used to determine differences in asthma symptoms between exercise protocols. All statistics were done in SPSS and statistical significance was declared at $p<0.05$.

5.4 RESULTS

A total of 16 participants were screened for participation. Two participants were excluded due to a drop in FEV_1 of <10% following the EVH challenge. One participant withdrew from the study after experiencing a 53% drop in FEV_1 following the EVH. The remaining 13 participants completed all five laboratory sessions (males=5; females:8). Results from the EVH challenge indicate the challenge was eucapnic with an average end tidal CO_2 of $5.5 \pm 0.18\%$. Participants were homogenous in terms of age and fitness level. Additional participant characteristics are shown in Table 1.

Lung Function

The decline in FEV_1 following the MICE was significantly greater as compared to the MIIE and HIIE ($p=0.016$ and $p<0.001$, respectively). There were no significant differences between HIIE and MIIE ($p=0.37$). Figure 2 displays the changes in FEV_1 following each of the protocols at each time interval post-exercise. No participants experienced a clinically significant drop in lung function following MIIE. Seven participants experienced a clinically significant drop in FEV_1 (≥10%) following the MICE protocol; an additional three participants had a drop of ≥ 8% (Table 2). One participant was unable to complete the entire MICE due to asthma related symptoms experienced at 10 minutes; however, the participant still experienced a lung function drop of 14.9%, after completing only half of the protocol. Of the three participants with small changes post-MICE, one was not able to complete the entire MICE session due to leg fatigue experienced at 8 minutes, another showed similarly small changes in FEV_1 following all three protocols. Of note, despite the small changes in FEV_1 following the MICE protocol in these two participants, the drop in FEV_1 following MICE was the greatest when compared to their data from the HIIE and MIIE sessions. The third participant who did not experience a significant drop in lung function following the MICE, did not experience a drop in lung function following any exercise session; this participant had a decline in 15% post-EVH and an ACQ score of 0.57, which was the lowest score among all participants indicating the best level of asthma control. Only two participants experienced a clinically significant change in FEV_1 following HIIE. These two participants also experienced the greatest decline in lung function following the EVH (-46% and -24.3%) and one had an ACQ score that was among the highest (1.85) for the sample while the other participant reported an ACQ score similar to that of the rest of the sample (1.42).

Intensity

Heart rate was lower during the MICE for the first seven minutes of the session in comparison to the MIIE and HIIE; however, heart rate continued to increase during the MICE and was higher than the heart rates achieved during the MIIE and HIIE. The heart rate response to each exercise protocol is displayed in Figure 3.

Adverse Events/Symptoms

One participant was not able to complete the full MICE protocol due to asthma related symptoms. Participants reported the greatest amount of symptoms following the MICE protocol in comparison to the HIIE and MIIE protocols at both 24 and 48 hours post-session. The most common symptoms reported were coughing, wheezing, and an increase in mucus production. A greater frequency of coughing, wheezing, and chest tightness ($p=0.007$; $p=0.035$; $p=0.035$, respectively) were reported at 24 hours post-exercise following MICE when compared to HIIE. Due to the low number of symptoms reported in the 48 hour log, statistical analyses could not be conducted; however, based on frequency of reporting, participants reported a greater amount of symptoms following the MICE in comparison to the HIIE and MIIE. Only 1 participant reported symptoms following the MIIE protocol. Additional details on self-reported symptoms following each protocol are shown in Figure 4.

5.5 DISCUSSION

The goal of this study was to compare the acute response to a single session of HIIE, MIIE, and MICE. The primary finding is that MICE leads to a statistically and clinically significant decline in FEV_1 post-exercise among adults with confirmed AHR. The secondary finding is that an acute bout of MICE is associated with greater self-reported symptoms at both 24 and 48 hours post-exercise when compared to HIIE and MIIE. These findings are the first to our knowledge to report on the acute response to different intensities of continuous and interval exercise sessions in adults with confirmed AHR and have important implications for exercise prescription in this population.

Our finding that interval exercise was associated with preserved lung function among adults with AHR is the first to our knowledge to report this in adults with EIBC. Limited research exists on the response to HIIE among adults with asthma. The literature that is available on this topic has focused on HIIE in the context of a warm-up. A review of these studies concluded that HIIE warm-ups showed the most consistent and effective attenuation of EIBC; however, HIIE in this study referred to sprint interval exercise (Stickland et al., 2011).

To our knowledge, there are no other studies that have looked at the acute response to HIIE in adults with confirmed AHR. Similar research exists in other respiratory conditions (Sabapathy, Kingsley, Schneider, Adams, & Morris, 2004; Butcher et al., 2013). In a study of 16 adults with moderate to severe COPD, participants completed a HIIE protocol at 70% of their anaerobic peak for 30 seconds followed by 2 minutes of recovery at 20% of their aerobic peak as well as a continuous exercise protocol at 80% of their aerobic peak. For both protocols, exercise was terminated based on symptom limitations. Results showed that participants were able to complete 170% more time and 95% more work during the HIIE protocol. Further, ventilation was lower during the HIIE, which may have contributed to the lower ventilatory limitation observed during this protocol (Butcher et al., 2013). Results from the studies listed above, and those of the current study, provide new knowledge and insight into the feasibility of HIIE as an exercise session among adults with EIBC.

While we did not collect data on ventilation during the exercise sessions, the HR during the MICE was higher at the end of exercise compared to HIIE and MIIE. In another study on adults with COPD, a similar trend was observed in the HR response to interval and continuous exercise protocols (Sabapathy et al., 2004) indicating that the ventilation during MICE in our study was likely higher than that in the interval protocols. The higher HR observed during the MICE as compared to the HIIE may be due to our protocol of 65% PPO, which may have been aggressive in a population with only moderate physical activity levels. However, it is possible that the recovery periods during the HIIE allowed HR to recover intermittently, which may further explain the differences observed in HR among exercise protocols. Additionally our HIIE protocol consisted of 90% PPO whereas the majority of the literature has focused on sprint-interval or 'all-out' exercise intervals, which may have contributed to the slightly lower HR during the HIIE protocol in the present study.

In addition to the role of a higher ventilation rate during MICE on the asthmatic response, previous research has also reported a strong correlation between breathlessness and metabolic load (VO_2), power output, and heart rate during progressive exercise among those with COPD (O'Donnell & Webb, 1993). This relation between breathlessness, which is a characteristic feature of asthma, and incremental/continuous exercise is of particular interest and may explain why one of the participants in the present study was unable to complete the MICE protocol and adds to the explanation of the decrease in lung function observed following the MICE protocol. It should be noted that participants in the present study had a ventilatory equivalent of oxygen (V_E/VO_2) of 38.4 ± 7.4 and a maximal voluntary ventilation (MVV) of 132.4 ± 34.3 L/min, which was similar to that documented in an asthma population who completed a 10-week step aerobic exercise intervention (Hallstrand, Bates, & Schoene, 2000).

Our finding that MICE was associated with a higher number and greater severity of late phase asthma symptoms are of particular interest. Controversy exists over the existence of a late phase reaction of EIBC following exercise. While some studies have reported a wide range of prevalence in the late phase reaction others have failed to demonstrate the occurrence of a late phase response (Verhoeff, Speelberg, van der Berg, Oosthoek, & Stijnen, 1990). In the present study, symptoms consistent with a late phase EIBC response were observed. Specifically, an increase in coughing, wheezing, chest tightness, and mucous production were among the most reported symptoms following the MICE and HIIE. In a recent systematic review completed in our laboratory, of the 21 included studies on exercise intensity and AHR, only four reported on any adverse or late phase asthma symptoms experienced (unpublished work). However, it remains unclear as to whether a late phase reaction did not occur or whether those data were not collected and/or reported. For the present study we used a self-report tool to determine the impact of the late phase asthma response; however, future research should look at the role of inflammatory markers in this response or create a validated tool to collect these data.

Limitations

Results of this study should be interpreted in light of the following limitations. First, continuous measures of ventilation were not obtained during the exercise protocols; therefore, we can only speculate on the increase in ventilation during the sessions. Second, this study was limited to adults between the ages of 18-44 years of age and participants all had relatively similar levels of asthma control; therefore, future research is needed in order to determine whether this response is similar across various age groups and among those with varying levels of asthma severity. Finally, the late phase asthma reaction was based on self-report symptoms; however, no valid or reliable tools exist for such data. Therefore, future research should assess inflammatory markers post-exercise to further elucidate the mechanisms responsible for the increase in symptoms following the MICE protocol.

In conclusion, it appears that MICE is associated with the greatest change in lung function and with the highest amount and greatest severity of late phase asthma symptoms, while interval exercise appears to be well tolerated in adults with mild-moderate asthma. Future research is needed in order to determine the mechanisms responsible for the preserved lung function following HIIE and the mechanisms responsible for the increase in symptoms following MICE. As well, the current study utilized a common HIIE protocol; however, additional research is needed to better understand the AHR response to various forms of interval training.

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Table 1. Characteristics of Participants that Completed all Five Sessions (n=13)

Characteristic	**Mean (SD)**
Age (years)	21.1 (2.7)
Height (cm)	167.4 (8.1)
Weight (kg)	73.4 (10.4)
Body Mass Index	26.5 (5.3)
Asthma Control	1.6 (0.5)
Resting Heart Rate (bpm)	73.0 (8.5)
Systolic Blood Pressure (mmHg)	120.7 (23.3)
Diastolic Blood Pressure (mmHg)	77.0 (5)
Maximal Ventilation (L/min)	112.4 (36.6)
Maximal Voluntary Ventilation (L/min)	132.4 (34.3)
Ventilatory Reserve (V_E/MVV)	0.8 (0.16)
Ventilatory Efficiency (V_E/VO_2)	38.4 (7.4)
V_E/VCO_2 Ratio	31.5 (6.5)
Maximal Oxygen Consumption (ml/kg/min)	34.6 (8.1)
Ventilatory Threshold (%)	69.6 (6.5)
Heart Rate at Ventilatory Threshold (bpm)	157.3 (13.3)
Peak Power Output (Watts)	184.6 (43.3)
Heart Rate Max (bpm)	186.9 (8.9)
Long Acting Medications	n=5

Table 2. Individual Data and Responses to the Protocols from each of the Five Visits (n=13).

Participant	ACQ Score	EVH Response	Reversibility from Visit 2	Maximal Change in FEV_1 post-MICE	Maximal Change in FEV_1 post-MIIE	Maximal Change in FEV_1 post-HIIE
P1	1.85	-14.9	3.2	-12.7	-7.3	-3.1
P2	1.42	-18.3	1.5	-14.9 ǂ	-3.7	-0.3
P3	1.85	-24.3	7.9	-30.2	-7.9	-16.0
P4	1.71	-13.7	4.9	-2.7	-4.3	-2.3
P5	0.57	-15	2.8	-3.6 ǂ	-0.2	0
P6	1.85	-21.7	3.4	-11.5	-3.0	-7.8
P7	1.71	-14.2	1.4	-15.3	-9.0	-3.5
P8	1.28	-15.8	7.7	-8	-4.1	-8.1
P9	2.85	-16.9	3.3	-9.6	-4.8	-8.4
P10	1.42	-46.0	37.6	-46.9	3.1	-30.4
P11	2.14	-14.5	1.6	-6.8	-5	0.3
P12	1.71	-23	10.7	-22.2	-8.7	-7.6
P13	1.00	-11.3	0.9	-8	-3.3	-5.2
Mean (SD)	1.6 (0.5)	-19.2 (8.9)	6.7 (9.7)	-14.8 (12.2)	-4.5 (3.3)*	-7.1 (8.3)*

ACQ: Asthma Control Questionnaire; EVH: Eucapic Voluntary Hyperventilation; MICE: Moderate Intensity Continuous Exercise; MIIE: Moderate Intensity Interval Exercise; HIIE: High Intensity Interval Exercise; *$p<0.05$ compared to MICE; ǂ participant did not complete the session.

Figure 1. Eligibility and Order of Laboratory Visits

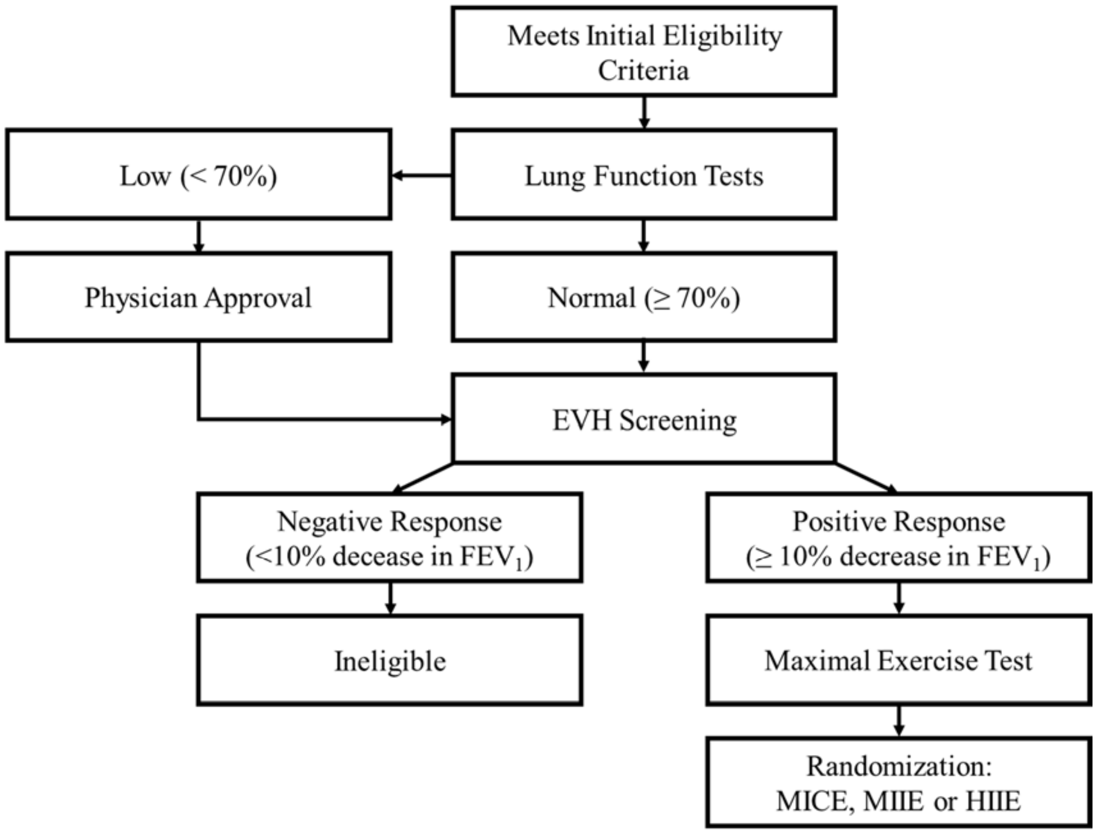
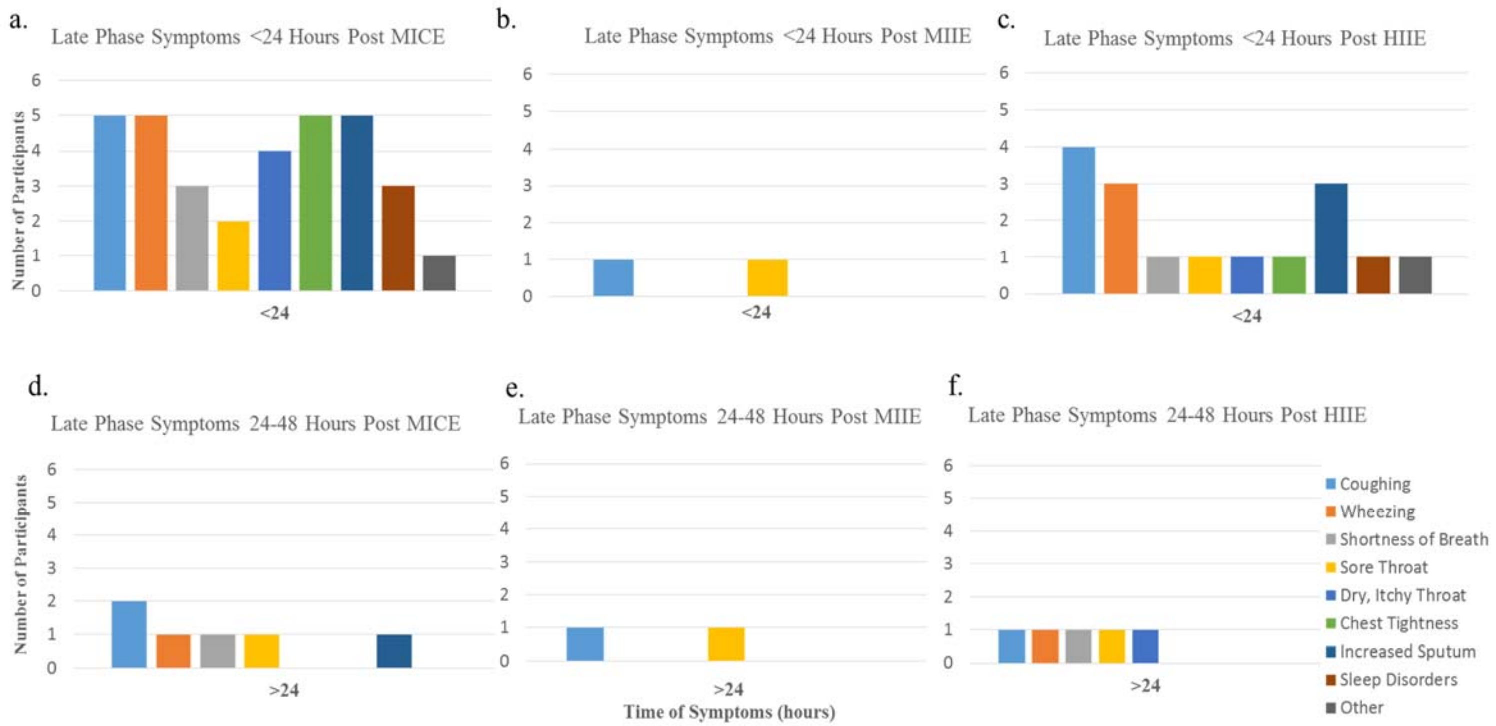


Figure 4. Self-Reported Symptoms 24 and 48 Hours After Exercise Sessions



CHAPTER 6: MANUSCRIPT 2

TITLE: SUBJECTIVE RESPONSES TO INTERVAL AND CONTINUOUS EXERCISE IN ADULTS WITH EXERCISE-INDUCED BRONCHOCONSTRICTION

Submitted to the Journal of Physical Activity and Health – Under Review

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6.1 ABSTRACT

BACKGROUND: Exercise leads to an increase in asthma symptoms among adults with exercise induced bronchoconstriction (EIBC), which may lead to lower activity levels among this population. The purpose of this study was to assess perceived exertion (RPE), perceived breathlessness (RPD), affect (FS), and physical activity enjoyment during and following an acute bout of high intensity interval exercise (HIIE), moderate intensity interval (MIIE) and moderate intensity continuous exercise (MICE) in adults EIBC. METHODS: RPD, RPE, and FS were assessed each minute during the sessions and enjoyment was assessed following each session (n= 13). RESULTS: RPE was lower during MIIE compared to HIIE and MICE (p=0.07; p=0.006). RPD was lowest during MIIE but was not different between HIIE and MICE. Affect was lower in MICE than HIIE in the last minute of exercise (p=0.003) and overall was greatest during the MIIE (p=0.022; p=0.018). Enjoyment scores were similar between protocols. CONCLUSIONS: Interval exercise is associated with lower ratings of perceived exertion and dyspnea, an increase in in-task affect, and similar physical activity enjoyment when compared to continuous exercise.

6.2 INTRODUCTION

Exercise-induced bronchoconstriction (EIBC) is characterized by symptoms of coughing, wheezing, and an increase in sputum production. It occurs in approximately 90% of adults with asthma (Weiler et al., 2007). EIBC occurs due to an increase in heat and water loss from the airways as a result of the high ventilation associated with aerobic exercise. These symptoms may help to explain why many adults with EIBC are not sufficiently active, given that these symptoms may lead to an increase in perceptions of discomfort, particularly breathlessness, and lack of enjoyment. Recent research suggests that the exercise-affect-adherence relationship and the potential for aversive affect during exercise may be of particular importance among those with EIBC. Specifically, affect during exercise can predict future engagement in that activity (Ekkekakis, 2003; Williams et al., 2008). As well, research indicates that exercise intensity plays an important role in exercise performance and can influence motivation to perform and continue exercise (Ekkekakis, Hall, & Petruzzello, 2005).

Physical activity engagement is important in individuals with asthma as research suggests that in addition to the vast benefits to general health, regular aerobic exercise can improve asthma specific outcomes, particularly asthma control (Dogra, Kuk, Baker, & Jamnik, 2011). Thus, in order to increase adoption and maintenance of exercise in this population, research is needed to better understand what intensity of aerobic exercise would be associated with the least amount of asthma related symptoms. Traditionally, exercise has been prescribed in the form of moderate intensity continuous exercise (MICE); however, the continuous nature of this exercise is associated with sustained high ventilation, which may lead to an increase in breathlessness and perceived exertion.

High intensity interval exercise (HIIE) is a popular and time efficient form of aerobic exercise, which is composed of brief bouts of high intensity activity followed by brief recovery periods. The present study was part of a larger study from our laboratory, which showed that interval exercise, both moderate and high intensity, is associated with fewer EIBC symptoms than MICE. Subjective responses of the participants to the different exercises were not reported in this study (O’Neill, Burgomaster, Sanchez, & Dogra, 2016).

Given the strong association between activity affect and activity participation, understanding the subjective responses to different types of aerobic exercise is important as it provides insight into their feasibility in individuals with EIBC. Therefore, the purpose of this study was to determine the subjective responses of exertion, dyspnea and feelings of affect and enjoyment following an acute bout of HIIE, moderate intensity interval (MIIE) and MICE in adults with EIBC. We hypothesized that MIIE would be associated with the least amount of perceived exertion and breathlessness but the most amount of enjoyment.

6.3 METHODS

Study Design and Participants

A randomized cross-over study design was used to assess differences between exercise protocols. Inclusion was limited to adults aged 18-44 years with a current prescription for rescue medication (i.e. short acting bronchodilator), to those who were meeting the minimum physical activity guidelines of 150 minutes of moderate to vigorous intensity physical activity per week, and to those with a drop in forced expiratory volume in 1 second (FEV_1) of 10% or higher following a eucapnic voluntary hyperventilation (EVH) challenge. Adults were excluded if they were considered highly trained to ensure that participants were not accustomed to high intensity exercise as this would impact their perceptions. All participants were appropriately screened (Canadian Society of Exercise Physiology, 2013) and provided written informed consent prior to laboratory testing. All procedures were approved by the Research Ethics Board of the University of Ontario Institute of Technology.

Procedures

Participants attended five laboratory session. Details of these sessions have been previously described. Briefly, the first session was used for the EVH test to confirm EIBC; the second session was used to measure maximal exercise capacity (peak power output) on a cycle ergometer; the third, fourth and fifth sessions were used for the three exercise protocols. Prior to each of these exercise sessions, participants were asked to refrain from consuming a heavy meal and caffeinated beverages for at least 2 hours. Additionally, participants were instructed to refrain from heavy exercise at least 24 hours prior to each exercise session. These instructions were given in order to minimize extraneous discomfort (i.e. gastrointestinal discomfort, muscle soreness) during the exercise protocols.

Measurements

Participants were asked to complete a demographic questionnaire which was used to collect information on age, occupation, physical activity levels, and mode of current physical activities. Additionally, participants completed an asthma control questionnaire during their first visit to the laboratory. This questionnaire has been shown to have strong evaluative and discriminative properties and can be used to measure asthma control with confidence (Juniper, O'Bryne, Guyatt, Ferrie, & King).

Exercise Protocols: Prior to each laboratory visit, participants were instructed to refrain from taking their short-acting medication for at least 8 hours prior to testing. Participants were fitted with a heart rate monitor and the cycle ergometer was adjusted for each participant. Participants were given a 5 minute warm up prior to each exercise session at 20 W and 70-80 rpm. Exercise sessions were: 1) MICE (65% PPO) for 20 minutes, 2) MIIE (65% PPO for 1 minute, 10% PPO for 1 minute repeated 10 times), and 3) HIIE (90% PPO for 1 minute, 10% PPO for 1 minute, repeated 10 times). Participants were instructed to cycle at 70-80 rpm throughout the entire session.

Perceived Exertion and Breathlessness

During the maximal exercise test, participants were familiarized with the Rating of Perceived Exertion (RPE) scale; RPE is used to assess subjective perceptions of effort during exercise. As well, participants were familiarized with the Rating of Perceived Dyspnea (RPD) scale; RPD is used to report perceived breathlessness during exercise. RPE was recorded each minute during each of the three exercise protocol sessions using the 6-20 Borg Scale; this scale has been shown to be a valid and reliable measure of exercise intensity (Chen, Fan, & Moe, 2002). RPD was recorded each minute during each of the three exercise protocol using the 1-10 RPD scale. The RPD scale has been shown to have high reliability and validity as well (Kendrick, Baxi, & Messier, 1987).

Affect

Participants were familiarized with the one-item feeling scale (FS) as a measure of general affect prior to their first exercise session. The FS was used to measure general pleasure and displeasure during each exercise protocol (Hardy & Rejeski, 1989). The FS has been shown to have high face, content, and construct validity (Kenney, Rejeski, & Messier, 1987; Rejeski & Best, 1987). Participants were informed at the beginning of each exercise session with the following: "While participating in exercise, it is common to experience changes in mood. For example, one might feel good and bad a number of times during exercise. When asked, please tell me how you feel in the current moment using the scale." The FS is scored on an 11 point bipolar scale ranging from -5 to +5. Affect was measured each minute during exercise.

Physical Activity Enjoyment Questionnaire

Participant enjoyment of each exercise protocol was assessed using a modified version of the Physical Activity Enjoyment Scale (PACES) at 10-15 minutes post exercise. This is an 18 item questionnaire scored on a 7-point bipolar scale. The original PACES has demonstrated high reliability and validity (Kendzierski & DeCarlo, 1991). The original PACES was modified by deleting one the following question: "I am very absorbed in this activity – I am not very absorbed in this activity." This modification was made due to the question being irrelevant at the time at which it was asked. Thus, the total scoring of the PACES was 119. Additionally, the original PACES instructions were modified from "Please rate how you feel at THE MOMENT about the physical activity you are doing" to "Please rate your enjoyment of the physical activity you did today." This modification was made to reflect the post-exercise time period in which the scale was administered. The PACES questionnaire has been used with the aforementioned modifications in previous work in high intensity interval exercise (Jung, Bourne, & Little, 2014).

Statistical Analyses

Means and standard deviations were used to describe the sample. A repeated measures two way analysis of variance with pairwise comparisons was used to determine differences within and between exercise protocols for affect, RPE, and RPD. Paired samples t-tests were used to compare the PACES scores between exercise protocols. All statistics were done in SPSS and statistical significance was declared at $p<0.05$.

6.4 RESULTS

Thirteen participants (males=5; females=8) with confirmed EIBC took part in the study. Participant characteristics can be found in Table 1. Two participants were unable to complete the full 20 minute MICE protocol due to leg fatigue (n=1) and asthma related symptoms (n=1); therefore, statistical analyses were based on the eleven participants that completed all protocols in their entirety.

RPE and RPD:

Differences in the average RPE among the three exercise protocols were observed ($F(1,10) = 728.3$, $p < 0.001$).The average RPE for the 20 minute protocol was significantly greater during the MICE compared to the MIIE (p=0.006) and was approaching significance when compared to HIIE (p=0.07). During the low intensity intervals there were differences in RPE between the HIIE and MICE (Figure 1); the difference was approaching significance when comparing the HIIE (11.3) to the MIIE (10.2, (p=0.052)).

Differences in the average RPD among the three exercise protocols were observed ($F(1,10) = 131.2$, $p < 0.001$). The average RPD for the 20 minute protocols was highest during the MICE (4.2 ± 1.59) as compared to MIIE and HIIE (1.7 ± 0.5, p = 0.001; 3.0 ± 1.2, p = 0.140 respectively). Although average RPD did not differ between the MICE and HIIE, differences were observed during each low intensity interval of the HIIE as compared to the MICE (Figure 2). Differences in RPD were observed when comparing the MIIE and HIIE (p=0.005).

Affect:

Differences in the average affect among the three exercise protocols were observed ($F(1,10) = 10.737$, $p=0.008$). Average affect was lowest during the MICE protocol (0.8 ± 1.3) as compared to the HIIE (1.5 ± 0.9, p=0.284) and MIIE (2.6 ± 0.4, p=0.022). Affect during the last minute of the MICE was lower compared to the HIIE (p=0.03). Further, affect was lower during the MICE as compared to the MIIE from minute 8 to the completion of the protocol (Figure 3).

PACES:

Physical activity enjoyment scores were lowest following the MICE (91.9 ± 17.3) and highest following the HIIE (98.4 ± 15.6); however, this was not statistically significant (p=0.10). There were no significant differences between the MICE and HIIE as compared to the MIIE (96.3 ± 11.4; p=0.15; p=0.45, respectively).

6.5 DISCUSSION

The purpose of this study was to determine the subjective responses of exertion, breathlessness, affect, and physical activity enjoyment following an acute bout of HIIE, MIIE, and MICE among adults with EIBC. The primary finding of this study is that interval exercise is associated with lower feelings of perceived exertion and perceived breathlessness as compared to traditional moderate-continuous type of aerobic exercise. The secondary finding is that in-task affect was higher during interval exercise when compared to MICE, but enjoyment was similar between all three protocols. These findings have implications for exercise prescription in adults with EIBC.

Our finding that RPE was lower during HIIE compared to MICE is consistent with previous literature. Specifically, it has been established that exertion increases over time during constant load exercise (Jones & Kilian, 2000). Additionally, our findings of a lower RPE during HIIE are supported by studies using healthy adults without asthma. Specifically, in a study of 20 participants (age: 22 ± 4 years) participants were asked to complete a 20 minute MICE protocol at 50% of their peak power output and 3 separate HIIE sessions varying in interval length (30 seconds, 60 seconds, and 120 seconds) at approximately 80% of peak power output for 1 minute followed by 10-20% peak power output for 1 minute. Results showed that the HIIE protocols were perceived as requiring less effort, except in the case of the 120s HIIE protocol, as compared to the continuous exercise (Kilpatrick et al., 2015). Interestingly, the 120s HIIE protocol elicited similar exertion scores as the continuous protocol, indicating that a shorter interval time may lead to lower perceptions of effort. These findings are particularly important given the research indicating that exercise tolerance is significantly limited by perceived effort (Marcora, Bosio, & de Moree, 2008).

The lower perceived exertion associated with HIIE may be explained in part by the recovery periods following the intense interval work as it allows for recovery of working muscles and cognitive recovery, which may further decrease the perception of muscular fatigue. This may also serve to partially explain the lower RPD observed during HIIE as compared to MICE. The recovery periods associated with HIIE may allow participants to "catch their breath", which may make it cognitively easier to complete interval exercise over time as opposed to MICE (Kilpatrick et al., 2015). Among adults with chronic obstructive pulmonary disease, RPD scores were significantly lower during interval exercise when compared to continuous exercise in a group of adults aged 65-71 years (Vogiatzis, Nanas, & Roussos, 2002). Thus, it appears that interval exercise is associated with less perceived exertion and breathlessness among those with EIBC, potentially making it a more palatable form of aerobic exercise than continuous exercise.

Conflicting findings of affect during HIIE have been reported in the literature; some studies have reported lower affect during HIIE as compared to moderate continuous exercise while others have reported the opposite (Saanijoki et al., 2015; Oliveira, Slama, Deslandes, Furtado, & Santos, 2013). In the present study, perceived exertion and breathlessness may have influenced affect and enjoyment of the protocols. Higher affect was reported during HIIE; this is supported by previous research, which compared HIIE (100% workload peak) to continuous 'vigorous' exercise (80% workload peak) among relatively inactive adults. Results indicated a tendency for higher in-task affect during HIIE towards the end of the exercise protocols, in line with results of the present study (Jung et al., 2014). The recovery intervals associated with HIIE may serve to partially explain the higher affect during this type of exercise. As previously mentioned, these recovery periods allow for breaks in the cognitive demands of intense exercise, which may be of particular importance given that mental stress increases perceptions of effort and reduces endurance performance (Marcora, 2009). Additionally, research on dread may help to explain the higher affect during HIIE, given the notion that some individuals prefer to get a painful stimuli "out of the way" sooner rather than later. In the context of HIIE and MICE, it is possible that participants prefer to complete a 'painful stimuli' (i.e. perceived exertion, perceived dyspnea) more quickly, as with HIIE, opposed to prolonged exposure to the same stimuli, as with MICE. Based on this and the research from

Kilpatrick et al (2015), which suggests that shorter HIIE intervals may be more preferable, future research should determine the impact of shorter interval lengths on perceived effort and in-task affect among those with EIBC (Kilpatrick et al., 2015).

With regards to the PACES scores, we found no differences between protocols. These findings are in contrast to research that has shown that participants experience higher enjoyment during HIIE when compared to MICE (Bartlett et al., 2011). The lack of differences observed in the present study may also be due to either the low sample size or the timing of the questionnaire. The participants were given the questionnaire 15 minutes post-exercise when their breath and heart rate had recovered; therefore, participants may have been feeling more comfortable in the moment at which they completed the questionnaire, which may have led to a less accurate depiction of enjoyment during exercise. Interestingly, similar findings have been reported in previous research comparing physical activity enjoyment between HIIE and continuous exercise (Oliveira et al., 2013; Jung et al., 2014). Specifically, in a study by Jung and colleagues (2014), the PACES questionnaire was modified in accordance with the present study and was also implemented post exercise (20 minutes post). The study by Jung and colleagues found no differences in enjoyment between their HIIE (100% Workload peak for 1 minute followed by 20% Workload peak for 1 minute) and moderate continuous exercise (40% Workload peak for 40 minutes) protocols (Jung et al., 2014). However, similar to the present study, the enjoyment mean was higher following the HIIE as compared to the MICE. Of note, the MICE in the present study was greater than that of the study by Jung and colleagues; however, exercise time was less.

Limitations

Results of the present study should be interpreted in light of the following limitations. First, the current study was composed of a small sample size; however, it was a homogenous sample of young, active adults with confirmed EIBC. Second, results of the current study were based on self-report i.e. cognitive mechanisms responsible for the present findings were not clear.

In conclusion, it appears that interval exercise is associated with lower ratings of perceived exertion and dyspnea, an increase in in-task affect, and similar physical activity enjoyment as compared to continuous exercise. Results from the present study suggest that interval exercise may be a preferred mode of exercise among those with EIBC and may lead to greater exercise adherence among this population.

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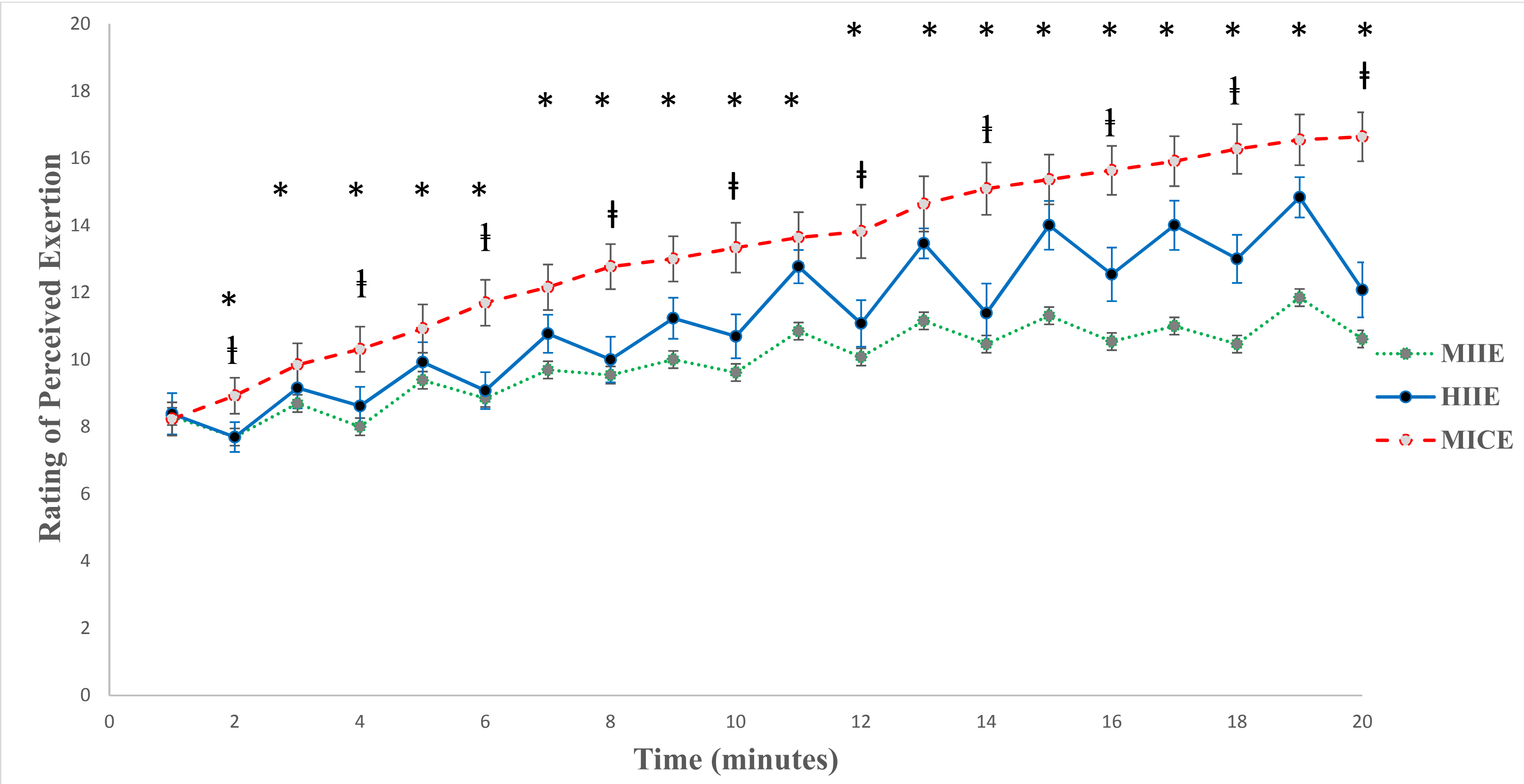
Table 1. Participant Characteristics (n=13)

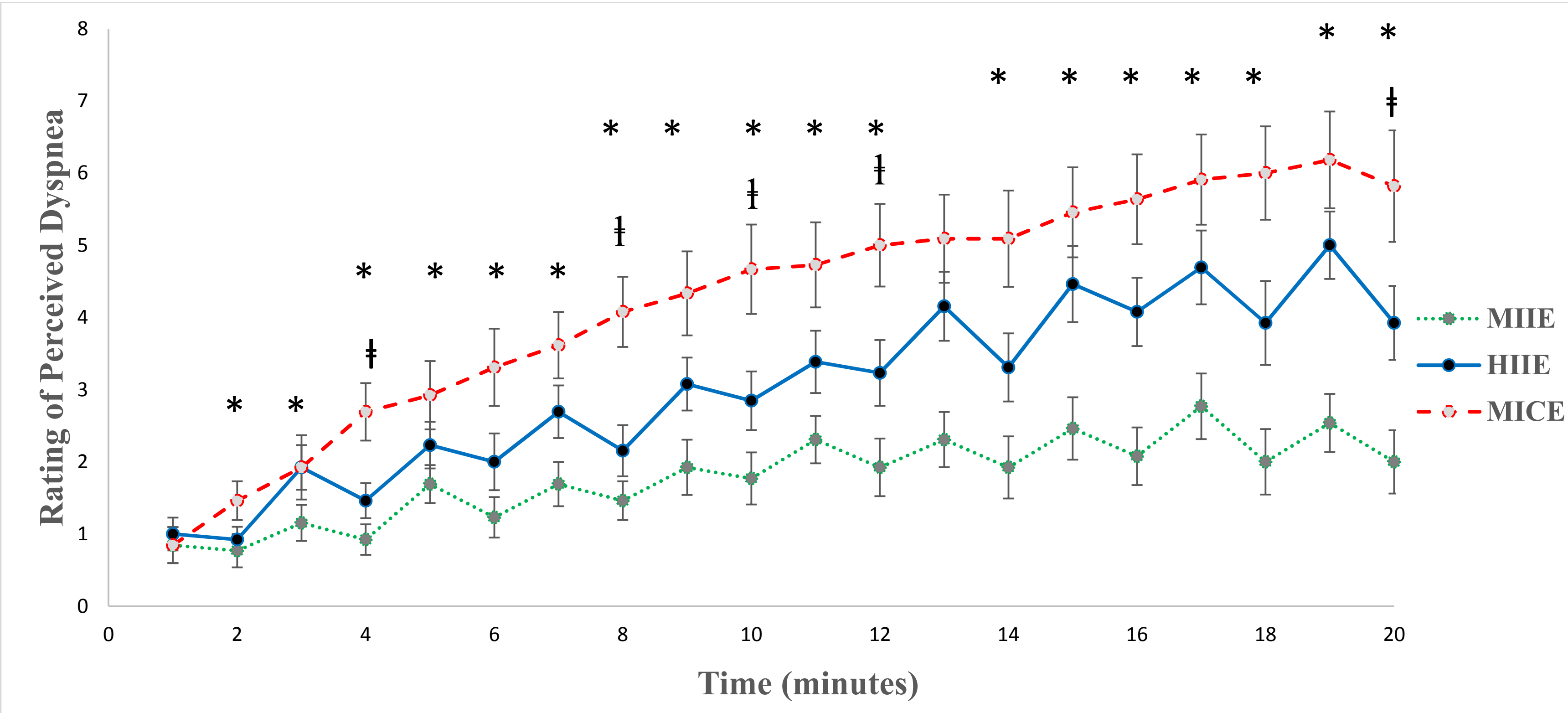
Characteristic	**Mean (SD)**
Age (years)	21.1 (2.7)
Height (cm)	167.4 (8.1)
Weight (kg)	73.4 (10.4)
Body Mass Index	26.5 (5.3)
Asthma Control	1.6 (0.5)

Figure 1. Feelings of Perceived Exertion during Exercise Protocols



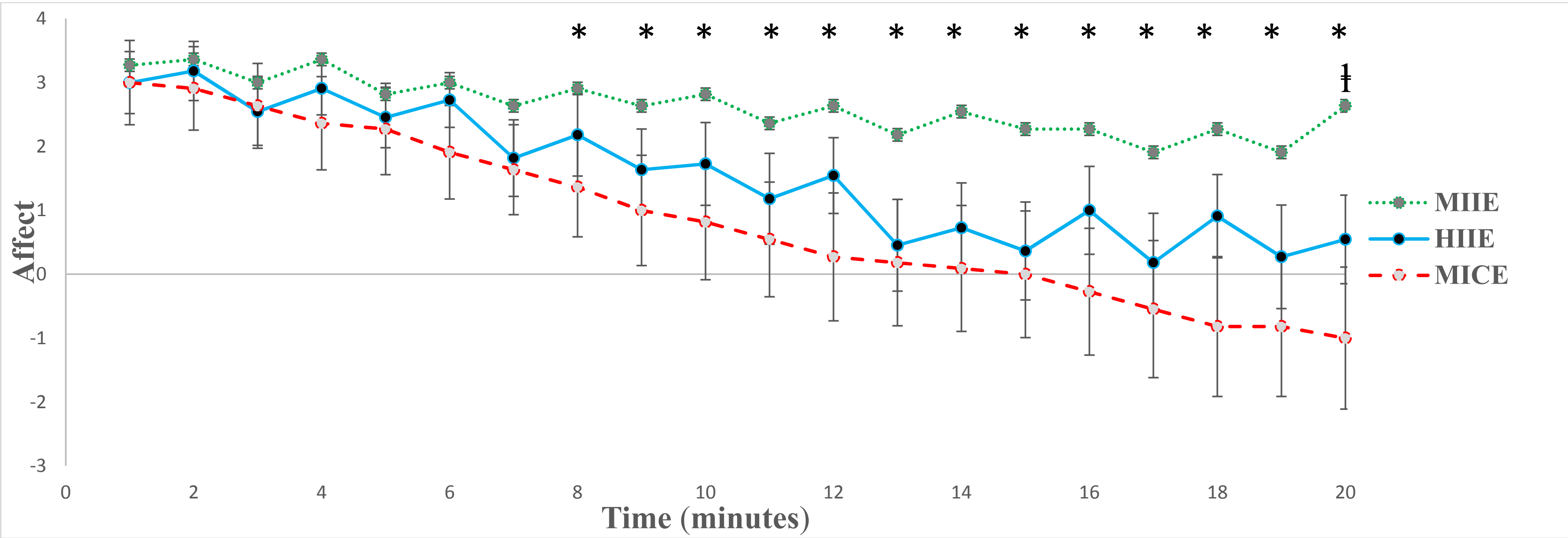
* p<0.05 between MICE and MIIE
ƚ p<0.05 between MICE and HIIE

Figure 2. Feelings of Perceived Dyspnea during Exercise Protocols



* p<0.05 between MICE and MIIE
ǂ p<0.05 between MICE and HIIE

Figure 3. Affect During Exercise Protocols



* $p<0.05$ between MICE and MIIE
ɨ $p<0.05$ between MICE and HIIE

CHAPTER 7: GENERAL DISCUSSION

7.1 THESIS SUMMARY

The primary objective of this thesis was to determine the acute response to HIIE among adults with EIBC. The main results indicate that lung function is preserved and late phase asthma symptoms are reduced following interval exercise as compared to continuous exercise. A definitive understanding of the mechanisms responsible for the preserved lung function and reduced late phase symptoms remains unclear. It is possible to speculate on these mechanisms, which may serve to partially explain our findings. For example, one possible explanation may be related to an increase in epinephrine secretion during HIIE. Research has shown that epinephrine secretion is increased during exercise and even more so during high intensity exercise (Trapp et al., 2007). Thus, an increase in epinephrine may have caused an increase in bronchodilation by binding to the $beta_2$ receptors in the airways.

It is also expected that the HIIE allowed for a reduced release of inflammatory markers, typically responsible for EIBC. The increase in ventilation during exercise increases heat and water loss from the lungs which has been shown to activate inflammatory markers such as mast cells (Gulliksson, Palmberg, Nilsson, Ahlstedt, & Kumlin, 2006). Mast cells and eiosinophils have been suggested to be play a large role as the cellular sources of the increase in cysteinyl leukotrienes observed in those with EIBC (Hallstrand, Moody, Aitken, & Henderson, 2005). Further, the eosinophil product eosinophilic cationic protein is released into the airways following exercise and mast cell degranulation occurs following an exercise challenge among those with EIBC (Mickleborough, Lindley, & Ray, 2005). Therefore, based on the results of a preserved lung function response during HIIE it is likely that the recovery intervals attenuated the release of these inflammatory markers.

The differences in heart rate observed may be explained by the re-establishment of parasympathetic tone during interval exercise. The recovery intervals may have allowed for heart rate to recover intermittently by reducing sympathetic activity and increasing parasympathetic activity (Kannankeril, Le, Kadish, & Goldberger, 2004). This intermittent heart rate recovery may have contributed to the reduced perceptions of effort and may have also contributed to the increase in exercise affect observed during interval exercise.

The aforementioned physiological responses potentially responsible for the preserved lung function during HIIE, may partially serve to explain the lower ratings of perceived exertion and breathlessness also observed during HIIE. Additionally, research has shown that dyspnea is a major component of overall perceived exertion (Noble & Robertson, 1996); therefore, the opening of the airways contributed to a reduced sense of breathlessness and exertion. It is possible that the greater sense of dyspnea observed during the MICE protocol may be partially explained by lung hyperinflation. The obstructive nature of asthma can cause air to become trapped in the airways causing the airways to hyper-inflate and create greater perceptions of dyspnea; however, it is important to note that this occurs only in the most severe cases (O'Donnell & Webb, 1993). The physiological response of the airways may also help to explain the higher affect reporting during interval exercise as opposed to MICE, given that a reduced sense of breathlessness and effort during exercise may lead to an improved emotional state.

These results provide novel insight into the physiological and psychological components of HIIE among adults with EIBC, which provide a wider understanding of the feasibility of HIIE among this population.

7.2 IMPLICATIONS

Results from this study have important implications for exercise prescription among adults with EIBC. Previous research clearly illustrates that many adults with EIBC are not sufficiently active (Ford, Heath, Mannino, & Redd, 2003). This low level of exercise adherence can be contributed to various barriers such as lack of time and an increase in asthma related symptoms both during and after exercise. Based on these barriers, the findings from the present study provide an exciting opportunity to minimize these barriers. HIIE has grown in popularity for a variety of reasons; however, perhaps one of the most important reasons is its' time efficient nature. Research has shown that 20 minutes of HIIE leads to similar and/or superior physiological adaptations as 40 minutes of traditional endurance exercise (Gibala et al., 2006). Results from this study provide promising insight into the tolerability of interval exercise given that it may preserve lung function among those with EIBC. As well, given that late phase asthma symptoms may be reduced following interval exercise this may help to increase long term exercise adherence. Further, lower perceptions of breathlessness and exertion during interval exercise, which is of particular concern among those with EIBC, may also aid in increasing regular exercise participation. The potential for this form of exercise to improve exercise participation rates among this population are of particular importance given that regular exercise has been shown to improve asthma control, improve asthma symptoms, and improve health related quality of life.

Overall, results from this study have important implications for improving exercise prescription and may contribute to the creation of specific and informed exercise guidelines for this population.

7.3 FUTURE RESEARCH

This was the first study to examine the acute responses to a HIIE session in adults with EIBC and provides preliminary knowledge of the tolerability of HIIE among this population. Future research is required in order to fully understand the mechanisms responsible (i.e. inflammatory markers) for the preserved lung function observed during HIIE. Additionally, in the present study ventilation was not monitored continuously; thus, it remains unclear as to whether differences in ventilation among the three exercise protocols is partially responsible for the preserved lung function.

Further, the present study implemented a common HIIE protocol, using a 1:1 ratio of work/rest; however, future research is needed in order to determine the acute response to HIIE using various work/rest ratios. For example, sprint interval exercise generally consists of 4 bouts of 30 second 'all-out' exercise separated by 4 minutes of rest (Gibala, Little, MacDonald, & Hawley, 2012). Research on this form of exercise has shown promising results on its' effectiveness among various chronic conditions; however, sprint interval exercise has not yet been studied among those with EIBC.

Although results from this study suggest that perceived exertion and dyspnea were lower and affect was higher during interval exercise, future research should determine whether these positive psychological outcomes can improve exercise adherence among this population.

7.4 LIMITATIONS

Results from this study should be interpreted in light of the following limitations. 1) Participants were given permission to take their short acting bronchodilators prior to the maximal exercise test; therefore, it is possible that the PPO calculated for the exercise sessions where medication was withheld was overestimated. This could serve to partially explain our findings. 2) Continuous measures of ventilation was not assessed; therefore, it is unclear whether the preserved lung function response following the HIIE was a result of a lower volume of ventilation in comparison to the MICE. 3) Inflammatory markers were not assessed; therefore, it is unclear the role that inflammatory markers had during each exercise protocol. 4) Total work completed during each protocol was as follows: MICE = 1300, HIIE = 1000, and MIIE = 750. Differences in total work across exercise protocols could help to explain the greatest decline in FEV_1 observed following the MICE since total work was greatest during this protocol. 5) Late phase asthma symptoms were assessed based on self-report measures and did not control for exposure to any additional triggers following the 48 hours post exercise session. Therefore, future research should control for additional triggers and thus, create a better understanding of the late phase asthma response following exercise and the mechanisms responsible for such response. 6) Although the sample size was sufficient in terms of assessing differences in the physiological outcomes, the sample size was low for assessing the psychological outcomes. This may explain the lack of differences observed in physical activity enjoyment scores among the exercise protocols.

7.5 SIGNIFICANCE OF THE STUDY

This study was the first to examine the response of a HIIE session among individuals with EIBC and provides a better understanding of the role of exercise intensity in adults with EIBC. Results from this study provide the first insights into the feasibility of HIIE within this population; therefore, filling an important gap within the exercise and EIBC literature. These results have important implications for improving exercise adherence among this population by providing a physiological and psychological basis for HIIE.

Further, results from this study will help to improve exercise prescription and inform exercise guidelines for this population.

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