ANAEROBIC PERFORMANCES AND ANAEROBIC CHARACTERISTICS OF ASTHMATIC CHILDREN

A DOCTORAL THESIS

DAVID BUTTIFANT

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DEPARTMENT OF PHYSICAL EDUCATION AND RECREATION
FACULTY OF HUMAN DEVELOPMENT
VICTORIA UNIVERSITY OF TECHNOLOGY

DEDICATION

To my darling wife, my most inspiring mentor. I am deeply grateful for your tremendous support, your love, our beautiful children and the patience that you have provided me throughout the many challenges of my life.

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ANAEROBIC PERFORMANCES AND ANAEROBIC CHARACTERISTICS OF ASTHMATIC CHILDREN

Abstract

The focus of this research was to examine the anaerobic characteristics and the related physiological effects of short-term, high intensity exercise on the asthmatic child. The research incorporated three studies that measured the physiological responses of asthmatic and non-asthmatic children to varied anaerobic stimuli. The first study examined a relatively recent method of anaerobic performance assessment, the Accumulated Oxygen Deficit (AOD), in pre-pubertal asthmatic males (mean age 10.9 years, $\dot{V}O_2$ peak 55.51 ml.kg.$^{-1}$.min^{-1}) as they ran to exhaustion at supramaximal intensities on a motorised treadmill. The results were compared to age-matched non-asthmatic children (mean age 11.1 years, , $\dot{V}O_2$ peak 47.04 ml.kg.$^{-1}$.min^{-1}). The findings from this study demonstrated that the asthmatic males displayed similar anaerobic performance characteristics compared with the non asthmatics. The protocol for the first study was not designed to identify whether high intensity exercise promotes the onset of EIA. The second study on the other hand, examined the influence of repetitive, high intensity exercise on asthmatic children (mean age 11.1 years). All tests in this study were conducted on a motorised treadmill with the grade remaining constant at 15 %. Continuous and intermittent speeds of the treadmill were predicted from a peak $\dot{V}O_2$ test to impose the same mechanical work over the same time for the differing protocols. Intermittent exercise was shown to be an equally potent stimulus for EIA compared with continuous exercise during this study. The final study compared the responses of a group of adolescent asthmatics and non asthmatics (mean age 15.04 and 14.53 years, $\dot{V}O_2$ peak 54.57 and 51.85 ml.kg.$^{-1}$.min^{-1} respectively) following repetitive high intensity cycling exercise. The duration of the exercise bout differed within a 30s work requirement with the exercise performed over different time demands of : 1x30s, 2x15s, and 3x10s. The results of these studies have contributed to the existing body of knowledge on exercise responses of young asthmatic males. The results demonstrated that there were no significant differences in the majority of selected measures of anaerobic performances between the asthmatic and non-asthmatic males who volunteered for this research. An interesting finding was made in the final study. The results of the blood borne indices of high intensity exercise displayed suppressed responses in plasma adrenaline levels and lactate levels in asthmatics compared to non-asthmatics following high intensity cycling. The results demonstrated significant differences in respiratory values post exercise between asthmatics and non asthmatics during the prolonged intermittent exercise. From these findings, it may be postulated that for the asthmatic children when compared to non-asthmatic, similar anaerobic performances (measured in mean and peak power output) are elicited via different mechanisms. The findings of this study also suggested that high intensity intermittent exercise at appropriate work rest intervals may be a provocating stimulus responsible for exercise induced asthma (EIA). The results demonstrated that there were no significant differences in the majority of selected measures of anaerobic performances between the asthmatic and non-asthmatic males who volunteered for this research.

Chapter One

Introduction

Chapter One

Introduction

Asthma is one of the most common chronic diseases of childhood (Bechler-Karsch 1994). Over 20% of Australian children have respiratory symptoms consistent with asthma. The increase in the prevalence of asthma has therefore created a major health problem in the Australian community (Mellis et al., 1991). According to Robertson et al. (1991), the current prevalence of asthma in Melbourne school children is high and has risen substantially over the past 26 years. It has been frequently documented that exercise remains one of the major extrinsic agents in the provocation of asthma (Godfrey, 1992, Lee, 1992) which is recognised as a clinical entity as exercise induced asthma (EIA). There has been considerable research effort put towards understanding this aspect of asthma consequently stimulating conjecture concerning the provoking stimulus (Anderson, 1988, McFadden, 1992). Considerable argument continues in the literature about the relationship between the mechanism linking exercise with bronchoconstriction and the relationship between the type of exercise and the influence towards EIA (Barnes, 1992, Bundgaard, 1984, Godfrey, 1974).

The majority of research conducted on the exercise responses of asthmatic have focused on post-exercise events of aerobic characteristics. Less is known therefore about the physiological responses of anaerobic performances of asthmatics during exercise. It has been postulated that asthmatics when compared to their non-asthmatics peers have diminished physical fitness (Bar-Or, 1986, Chryssanthopoulos et al., 1979, Clark, et al., 1988, Ludwick et al., 1986, Varray et al., 1989). Other studies however have demonstrated that asthmatics can achieve similar levels of aerobic fitness compared to non-asthmatics (Bevegard et al., 1976, Fink et al. 1993, Garfinkel et al., 1992, Ingemann-Hansen et al., 1980). In contrast to the number of studies on aerobic performances of asthmatic subjects, there has been little research examining the anaerobic characteristics of asthmatics and their respiratory responses from high intensity exercise (de-Bisschop et al., 1992, Inbar et al., 1981, Karila et al., 1992). Karila et al. (1992) examined the maximal anaerobic power of asthmatic children and indicated that asthmatics had a lower anaerobic power than their non-asthmatic counterparts. The minimal research focusing on anaerobic performances of asthmatics creates limitations on substantiating evidence to identify whether asthmatics have lower anaerobic power compared to non-asthmatic subjects. High intensity bouts of exercise are very common amongst children's play activities which utilise anaerobic pathways. These natural play activities of children (Cooper, 1993) and the demands of popular team sports involve intermittent efforts of high intensity (Naughton, & Carlson, 1990) and are often very short term and supramaximal in relation to the individual's maximum aerobic power ($\dot{V}O_2max$). It has been well documented that continuous exercise provokes exercise induced

asthma, (Godfrey, 1992, 1974, Silverman and Anderson, 1972), however continuous exercise is not a characteristic of a child's spontaneous play patterns and popular sporting choices. These factors therefore support the need for further investigation into the short-term responses of high intensity exercise on the asthmatic child.

Purpose

As it has been observed that children are engaged regularly in anaerobic activity, it became the purpose of this investigation to:

1. Compare anaerobic performances of asthmatic and non-asthmatic young males using the accumulated oxygen deficit method and modifications of the traditional Wingate Anaerobic Test.

2. Examine the influence of repetitive, high intensity work (6 minute duration) on the post exercise respiratory responses on children with exercise induced asthma.

3. Investigate blood borne indices of anaerobic metabolism and respiratory responses in asthmatic adolescents following a number of different short term high intensity exercise tests of less than 1 minute duration.

Rationale

The rationale behind this research argues the need to investigate the physiological effects of anaerobic exercise in the asthmatic child when compared to their non-asthmatic counterparts. The study further recognised the challenge to apply the accumulated oxygen deficit technique as a measure of the maximal anaerobic performance because it had not been investigated within asthmatic populations. It is also argued that these investigations will contribute to a greater understanding of the influence of high intensity exercise as a provoking stimulus to exercise induced asthma.

Limitations

The limitations of the investigations were as follows:

1. There was no attempt to control dietary habits, physical activity patterns, and psychological influences outside the testing environment.

2. Moral and ethical constraints were imposed on the quantity of tests selected in each study. Constraints were also extended to the nature of appropriate procedures presented to subjects. For example invasive procedures such as muscle biopsies were excluded from this research.

3. Volunteers could only be recruited with their own permission and that of their parent/guardian. Therefore the studies do not represent a randomised sample of asthmatic children in the population. The studies were also limited to "normal" and "healthy" children who were either asthmatic (experimental) or non-asthmatic (control). For each of the studies the asthmatics who volunteered do not reflect a randomised selection of the asthmatic population.

Delimitations

1. The studies were delimited to two age groups of subjects who volunteered from pre-adolescent and adolescent populations.

2. All testing was conducted under standardised laboratory environmental conditions and may not as such represent realistic environmental conditions.

3. In the first study pre-adolescent males were restricted to a pubertal ranking of Tanner Stage 1 for pubertal hair (1962). This group of children had a chronological age range of 10 - 11 years of age.

4. In the second study pre adolescent children were restricted to a pubertal ranking of Tanner Stage 1 and 2 for pubertal hair (1962). This group of children had a chronological age range of 10 - 12 years of age.

5. In the third study, adolescent subjects reported their pubertal development from stages 2 to 5 on the Tanner scale for pubertal hair and genital development (1962). Their ages ranged between 13 and 16 years.

Definitions

The following terms were defined in accordance with their particular usage in this research:

Anaerobic function measures

All-out - The maximal volitional work effort at all times.

Anaerobic capacity - Estimations of maximum amount of ATP formed by anaerobic processes [creatine phosphate hydrolysis and lactate production] during exercise.

Supramaximal - The amount of work or exercise intensity in excess of the power equivalent of the maximal oxygen uptake.

Maximal accumulated oxygen deficit - The difference between the predicted oxygen cost for supramaximal intensity exercise and the actual accumulated oxygen uptake achieved throughout the duration of the time to exhaustion. Medbo et al. (1988), defined maximal accumulated oxygen deficit as a "capacity" because they observed a plateau of the anaerobic contribution to exercise where performed over a range of supramaximal intensities. Accumulated Oxygen Deficit is expressed as an equivalent volume of oxygen in $ml.kg^{-1}$ or in total litres.

Power - The rate of doing work; the rate of transfer of energy. It is defined in watts (W). 1 watt = 1 joule per second ($1\ W = 1J \cdot s^{-1}$)

Mean power - The average power sustained throughout the duration of a cycle ergometer test. It is expressed in absolute and relative, terms (watts and watts per kilogram of body mass).

Peak power - The highest mechanical power produced during any 3- to 5- second period.

Anthropometric measures:

These terms refer to body size, composition and structure measures (Lohaman):

Height (cm) - A vertical measurement of a structure, from bottom to top, when it is placed or projected in an upright position.

Mass (kg) - The physical property of matter that gives it weight and inertia.

Body Mass Index - The ratio of body mass (in kilograms) to height (in centimeters) squared : BMI = wt (kg)/ ht (m) ^{2}.

Skinfold measurements - A measure of the amount of subcutaneous fat, obtained by inserting a fold of skin into the jaws of a caliper at pre-determined sites on the body.

Cardiorespiratory function measures

Maximal oxygen uptake ($\dot{V}O_2$max) - The maximal rate of oxygen utilised by a subject during an incremental test (eg. running and cycling) to volitional exhaustion. It is expressed in absolute terms ($l.min^{-1}$) and in relative terms, as a function of body mass ($ml.kg.^{-1}min^{-1}$)

Peak oxygen uptake ($\dot{V}O_2$ peak) - The peak rate of oxygen utilisation of a child during a running or cycling incremental exercise test to volitional exhaustion or the achievement of predetermined maximal criteria which have been observed previously (Zwiren, 1989). It is expressed in absolute terms ($l.min^{-1}$) and in relative terms, as a function of body mass ($ml.kg.^{-1}min^{-1}$). This measurement is widely accepted in the paediatric exercise science fraternity.

Steady state - It is the level of oxygen uptake during submaximal exercise which demonstrates a plateau in the measure of energy utilisation during this submaximal exercise.

Respiratory Physiology

Acidaemia - A relative excess of hydrogen ions in the blood

Airways obstruction - Narrowing or occlusion of airways

Alkalaemia - A relative deficiency of hydrogen ions in blood

Anoxia - Absence of oxygen

Apnoea - Cessation of breathing

Bradypnoea - Decreased frequency of breathing

Bronchoconstriction - Airways obstruction due to an increase in tone of bronchial smooth muscle

Dyspnoea - A consciousness of difficulty in breathing

Hyperpnoea - An increase in ventilation relative to the metabolic rate

Hypocapnia - A relative low tension of carbon dioxide in the blood.

Hypoventilation - A reduction in ventilation sufficient to cause hypercapnia

Hypoxaemia - A relative deficiency of oxygen in blood

Hypoxia - A relative low tension of oxygen at a specified site

Spirometry - The measurement of lung capacities and flow rates

Steady state - The condition of equilibrium for a particular variable

List of Abbreviations and Symbols

FVC	forced vital capacity (litres)
FEV_1	forced expiratory volume in 1 second (litres)
FEV_1/FVC	percentage expired (i.e. 100 x FEV1/FVC)
MVV	maximal voluntary ventilation (litres. min^{-1})
MMEF	maximal mid-expiratory flow rate (litres. s^{-1})
$FEF_{25-75\%}$	mean forced expiratory flow during the middle half of the FVC ($1s^{-1}$)
Raw	resistance of tracheobronchial tree to flow of air into the lung $\left(\frac{cmH_2O)}{litres/sec}\right)$
$\dot{V}O_2$	rate of oxygen uptake per minute
$\dot{V}CO_2$	amount of carbon dioxide eliminated per minute
$\dot{V}_E$	minute ventilation
PO_2	partial pressure of oxygen
PCO_2	partial pressure of carbon dioxide
FEO_2	fraction of oxygen in expired air
$FECO_2$	fraction of carbon dioxide in expired air
RER	respiratory exchange ratio
μ	viscosity of gas
P_B	atmospheric pressure
Hb	hemoglobin
HCO_3^-	bicarbonate ion
ADP	adenosine diphosphate
ATP	adenosine triphosphate
EIA	exercise induced asthma
EIB	exercise induced bronchospasm

BTPS	body temperature and pressure
ATPS	ambient temperature and pressure saturated with water vapour
a	arterial blood
v	venous blood
c	capillary blood
RH	relative humidity
WC_i	water content of inspired air (mg H_2O L^{-1} air)

Chapter Two

Review of Literature

Sub-headings

- Overview Pathogenesis of EIA
- Characteristics and Diagnosis of Exercise Induced Asthma
- Testing Procedures for EIA
- Witholding Medication and the Effects of Anti-Asthmatic Medication
- Catecholamines
- Section Summary
- Refractory Period
- Anaerobic Metabolism
- Anaerobic Characteristics of Children
- Various Types of Exercise Responses with Asthmatics
- Short-Term High Intermittent Exercise
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- Maturational Indices
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- Conclusion

Chapter Two

Review of Literature

Overview

The term asthma has been given various definitions by authors and there is still much debate over its best definition. Asthma is described by Morton and Fitch (1993), as a disease characterised by an inflammation of the airways, which is typified by mucosal infiltration with inflammatory cells (especially the eosinophils), thickened airway walls, spasm of the bronchial smooth muscle, oedema, hypertrophy of glands and smooth muscle, damaged epithelium and increased production of mucous. According to Barnes et al. (1989), chronic inflammation in asthma results from the infiltration of large numbers of inflammatory cells and the actions of inflammatory mediators which are subsequently released. The pathological changes to the bronchial mucosa are usually described as:

1. Oedema of the bronchial mucosa, which decreases the diameter of the airways.
2. Disruption of the epithelial layer of the mucosa.
3. Hypertrophy and contraction of smooth muscle.
4. Increased production and hypersecretion of mucous.

Sheth and Lemanske (1991), contended that the concepts of reversibility and hyper-responsiveness have been appreciated for some time, and that asthma being viewed as an inflammatory lung disease has only recently received appropriate emphasis. There is good evidence that the degree of bronchial hyperreactivity may be the key feature of clinical asthma. This characteristic is related to the amount of inflammation of the bronchial mucosa (Chung, 1992). Kumar and Busse (1995) stated that at the end of the 19th century, asthma was viewed as a form of "bronchitis" and was thought then to be an inflammatory disease. Godfrey (1993), reported "asthma as a common disease of children the basis of which is a state of chronic immunological inflammation which causes bronchial hyper-reactivity and renders the patient liable to develop widespread airways obstruction in response to a variety of stimuli." He stated further that immunological inflammation resulted from ongoing antigenic stimuli, with the release of chemical mediators responsible for short-term bronchospasm and that the cytokines were responsible for the ongoing inflammatory process. Lee (1992), described asthma as being characterised by bronchial hyper-responsiveness influenced by precipitating factors. These precipitating factors include specific allergens acting via sensitised mediator cells through an IgE-dependent mechanism. Immunoglobin IgE is produced by plasma cells and lymphoid tissue and binds to mast cells in the bronchial muscle. It has been acknowledged that there are many inflammatory mediators that may have an effect on airway smooth muscle by releasing bronchoconstrictor mediators from other inflammatory cells.

These mediators consist of receptors associated with histamine, prostanoid, leukotriene, platelet activating factors, adenosine and bradykinin. It is most likely a network of mediators contribute to asthma. It is however unlikely that all cells are activated by the same inflammatory stimulus. These mediators have various effects on the target cells within the airway which subsequently cause contraction of airway smooth muscle, either directly or indirectly via other mediators, or through activation of neural pathways (Chung and Barnes, 1992). It has been proposed that neural control of the airways may be abnormal in asthma and neurogenic mechanisms and thus may contribute to the pathophysiology of asthma. The shedding of the airway epithelium may expose sensory nerve endings and consequently be triggered or sensitised by certain mediators. Chronic asthma may amplify the inflammatory process and subsequently change neural function irreversibly. This condition may further result in peripheral nerves retaining a permanent 'memory' of this inflammation (Barnes, 1992). Unfortunately, a precise understanding of asthma has been impeded by a failure to accept a universal definition for asthma among researchers (Sheth and Lemanske, 1991). It has been reported by Pride (1992), that there have been two different approaches to the definition of asthma; one emphasising the role of allergic pathogenesis consisting of atopy, raised IgE and eosinophilia, and the second approach avoiding pathogenesis and focussing diagnosis on variability and periodicity of symptoms, signs and airway obstruction. Cade et al. (1988) defined asthma as a recurrent, reversible, generalised airways obstruction, and associated it with increased bronchial reactivity. Many authors agree that it is a reversible obstructive airway disorder. According to the American Thoracic Society (1962), asthma is a disease characterised by an increased responsiveness of the tracheobronchial tree to a variety of stimuli. These stimuli have been identified by Kumar and Busse (1995), as exercise, cold air, irritants, aspirin, occupational exposure to dust or fumes, allergens, and viral infections. The responses to these stimuli result in widespread narrowing of the airways which changes in severity either spontaneously or as a result of therapy.

Investigations of asthma have been documented from as early as the first and second centuries AD, Arataeus of Capadocia hypothesised that vigorous exercise or activity triggered symptoms of asthma. He stated, "If from running, gymnastic exercises, or any other work, the breathing becomes difficult, it is called asthma." (Adams, 1856). This hypothesis was supported in 1698 by an English Physician, Sir John Floyer. Being an asthmatic himself, he wrote, "All violent exercise makes the asthmatic to breathe short." Almost two hundred years later in 1864, another English Physician H.H. Salter postulated that a rapid passage of fresh and cold air over the bronchial membranes might trigger a response by directly irritating the nervous system (Sly, 1986). Jones et al. (1962), provided the first modern clinical description of exercise induced asthma (EIA). This was documented after he tested asthmatic children running with "sufficient" severity of intensity and duration to display similar patterns of post-exercise bronchoconstriction.

Anderson et al. (1975) extended the work of Jones et al. (1962) and described EIA as an increase in airway resistance that occurs after 6-8 minutes of strenuous exercise, it was described as causing a

transient hyperinflation and arterial hypoxemia in most people with asthma. McFadden and Gilbert, (1994) described EIA as a condition in which vigorous activity triggers acute airway narrowing in people with heightened airway reactivity. Although these definitions of EIA from Anderson and McFadden are similar, their postulated pathogenesis of EIA differ.

Pathogenesis of EIA

Various claims and counterclaims exist about the pathogenesis of EIA. Anderson (1984), is of the belief that evaporative water loss causes a transient increase in osmolarity, consequently causing the airways to narrow. McFadden (1990) maintained that this narrowing occurred when the airways were rapidly rewarmed by reactive hyperaemia of the bronchial circulation. Godfrey (1992) states that EIA can be considered as a sequence of events that require, a receptor site for the triggering stimulus, an intermediate pathway and an effector mechanism. He expressed concern that some investigators have tended to overlook these requirements or to fail to distinguish between them, while others have heavily disputed each of the components of the system. McFadden (1990) postulated that the development of airway obstruction in EIA was related to the thermodynamic events that occur within the airway during or after hyperpnea. He proposed that EIA was a result of "rapid expansion of the blood volume of peribronchial plexi" and his hypothesis proposed that the development of exercise induced asthma relied on the thermal gradient in the airways at the end of hyperpnoea. Previously, McFadden et al. (1985) investigated the intrathoracic thermal events that occurred throughout breathing in six normal subjects with the mean age of 30.7 years. A flexible probe containing multiple thermistors was inserted into the tracheobronchial tree with a fibreoptic bronchoscope. He theorised high ventilation when combined with the low temperature of inspired air, pushed the conditioning process from the upper to the lower airway and thus caused a movement of heat and water from the mucosa. He argued that the greater the quantity of thermal energy that is needed to be transferred, the cooler the airways would become, and that the quicker they rewarm, the greater the bronchi were narrowed. McFadden (1992), further acknowledged that it is not known why the intra-airway thermal fluxes produced bronchial narrowing. He did however consider Anderson's (1985) findings plausible in that he accepted that rapid breathing may initiate evaporation of mucosal surface water and an that increase in osmolarity may cause mast-cell degranulation and constriction of airway smooth muscle. He challenged this hypothesis however, because he believed that there is not strong supporting evidence to prove that airway drying develops.

Gilbert et al. (1987), measured the water content, water flux and osmolarity in asthmatic and non-asthmatic subjects, in the posterior pharynx, glottis, mid trachea, carina, right lower lobe bronchus, and anterior segmental bronchus. The findings indicated that heat, water flux and osmolarity demonstrated no differences between the asthmatic and non asthmatic subjects post exercise. In a review of the research by Gilbert et al., (1987) and other investigations on osmolarity, McFadden and Gilbert (1994) advocated that exercise-induced asthma was a mechanical event in which the airways

were rapidly rewarmed by reactive hyperaemia of the bronchial circulation with subsequent oedema of the airway wall. Thus it appears that McFadden and colleagues proposed that EIA depended on the thermal gradient in the airways created by an increase in ventilation. McFadden and Gilbert (1994) and Gilbert et al. (1987) demonstrated that the severity of EIA was not solely reliant on airway cooling but was also dependent on the speed and amount of post challenge airway re-warming which result in bronchospasm.

As previously discussed Anderson (1993), stated that ".... the stimulus for the increase in airway blood flow is an increase in osmolarity of the airway submucosa. This osmotic change is caused by the movement of water to the airway lumen in response to evaporative water loss during hyperpnoea. The increase in airway blood flow may occur directly or indirectly by the osmotic release of mediators. Exercise induced asthma is most likely to be due to the contraction of the bronchial smooth muscle caused by the same mediators. Whether it is enhanced or inhibited by alterations in airway blood flow is not established in man". In support of Anderson (1993), Ferrus, et al. (1980) demonstrated that throughout strenuous exercise there is a significant increase in ventilation which involves recruitment of the large airways to provide the extra heat and water required for conditioning the inspired air. It had been previously shown that loss of water by evaporation from the respiratory tract reduced airway mucosal temperature and increased the ion concentration of the perciliary fluid (McFadden et al., 1982, Man et al., 1979, Potter et al., 1967). These events occur simultaneously however, it is difficult to ascertain whether it is the cooling of the mucosa or the development of hyperosmolarity of the perciliary fluid that stimulates EIA (Anderson, 1988). Similarly, Noviski et al. (1988), proposed that respiratory heat loss or water loss have been possible triggering factors in exercise and hyperventilation-induced asthma and that exercise intensity and climatic factors were both important in determining the severity of EIA. The investigation involved eight young asthmatics who performed both exercise and isocapnic hyperventilation manouevres under similarly controlled conditions. From their findings they concluded that while the hypernoea in exercise may serve as a trigger, exercise per se introduced an additional factor which served to limit the full response observed with isocapnic hyperventilation. They further suggested that this attenuated response was revealed at low ventilatory levels but may have been masked in high intensity exercise demands.

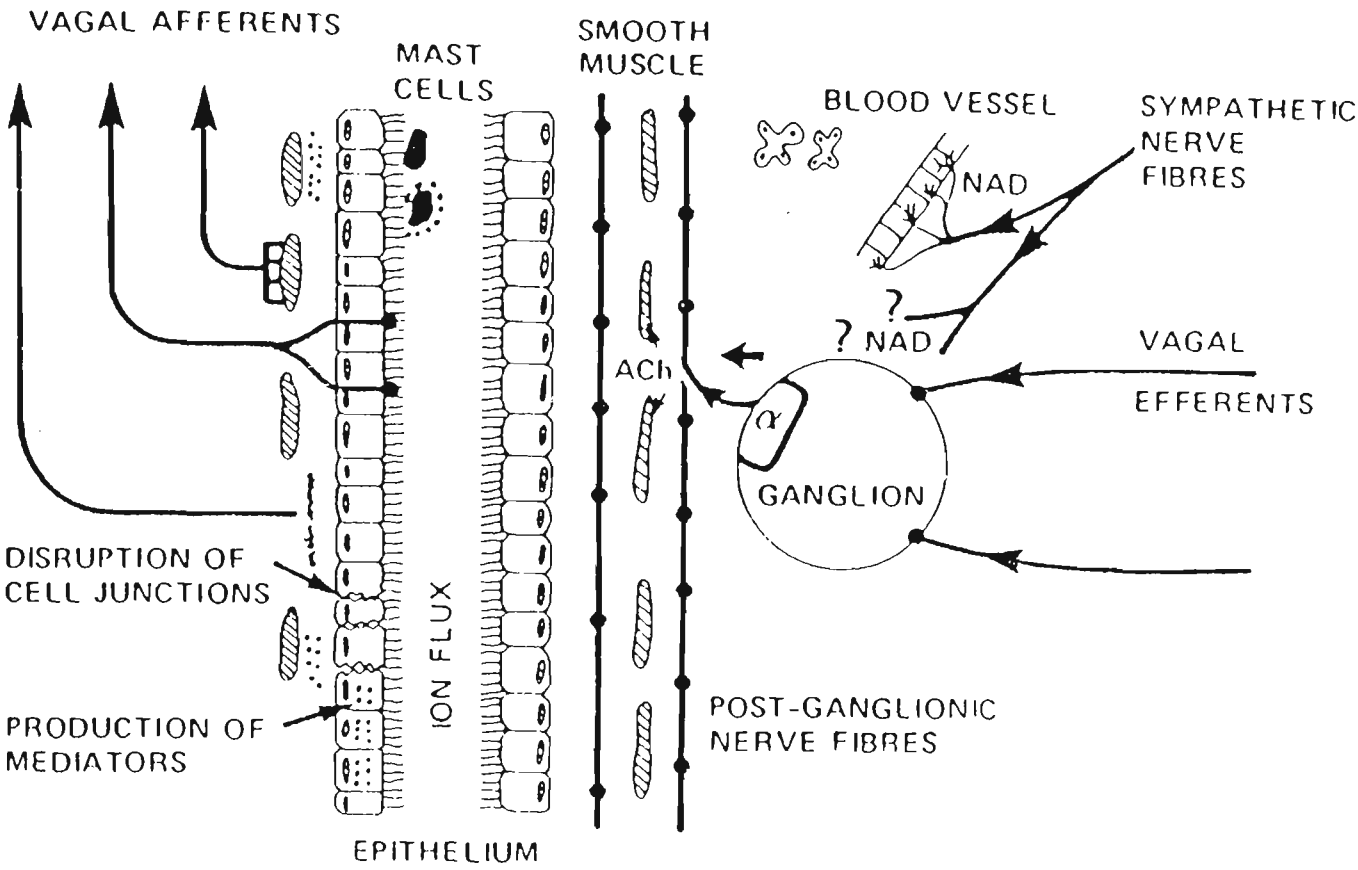
There is substantial evidence to support the argument that the effects of drying are more influential than cooling on the incidence of EIA and that a reduction in the temperature of the bronchial mucosa may not be a primary stimulus to EIA (Anderson, 1984, 1985, 1988, and Hahn et al., 1984a). Hahn et al. (1984b) conducted an investigation on ten asthmatic males with a mean age of 21.8 years who performed four separate eight-minute treadmill runs in an environmental chamber. The air was conditioned to an inspired air temperature of either 9-10°C or 35°C, with the inspired water content per litre of air of 9-10mg H_2OL^{-1}. The authors demonstrated that changing the inspired air temperature by 25°C had no influence on the post exercise reduction in peak expiratory flow rate (PEFR). From this finding Hahn et al., (1984b) postulated that drying of the airway, rather than

cooling was the mechanism responsible for EIA. This was confirmed by Aitken et al. (1985) who demonstrated that osmotic changes in the respiratory mucosa can result in bronchospasm. Thus the aforementioned investigators would suggest that osmotic changes appear to be associated more with drying than cooling of the airways.

A study conducted by Daviskas et al. (1990) involved a mathematical model of the heat and water vapour transport in the human respiratory tract for mouth breathing. It was devised to calculate the "local" quantities of heat and water transfer in the airways. They confirmed that the mathematical models of heat and water loss from the airways supported the potential for substantial loss of water from below the pharynx. The rate at which water is returned to the airways may not be capable of maintaining the periciliary fluid isotonically and subsequently the intrathoracic airways may become significantly dehydrated during increased ventilation rates. Smith and Anderson, (1989) tested 17 asthmatic males aged between 12 and 17 years who performed exercise tests on a bicycle ergometer at 75% of their predicted maximal workload for a duration of between 5.5 -10 minutes. The purpose was to compare the changes in FEV_1 induced when the rate of re-warming of the airway after exercise was increased with or without the potential for inspired air to cause additional condensation in the airway. The exercise tests required the subjects to breathe at various inspired air temperatures and inspired water content (mg H_2OL^{-1}) during the exercise and recovery. These conditions ranged from -15°C to 50°C for the inspired air and 0 to 44 mg H_2OL^{-1}. From their results the authors concluded that a temperature gradient and rapid re-warming of the airways was not necessary to provoke airway narrowing. This was not consistent with the hypothesis from McFadden and collegues (1982, 1985, 1990, 1992) that rapid airway re-warming causes EIA. Neither the change in osmolarity of the epithelial fluid nor the reduction in temperature of the airway mucosa have substantially proven to be a causative mechanism of EIA. The commonly accepted concepts appear to be that reflex bronchoconstriction is mediated by vagal parasympathetic nerves and the subsequent release of substances which contract bronchial smooth muscle, either directly or through post ganglion nerves are associated with EIA (Anderson, 1993). It is hypothesised that the loss of heat and water, cause a release of leukotrienes from epithelial cells which increase the release and action of other mediators from mast cells in the submucosa and thus, may also contribute to EIA.

Several authors believe that the drying of the bronchial mucosa as a result of increased ventilation is most likely to trigger EIA and subsequently that this drying effect results in the liberation of mediators from mast cells (Anderson, 1984, Lee et al., 1982). According to Anderson (1985), there are a variety of sites in the airways where an increase in osmolarity from evaporative water loss may act as a stimulus to induce airway narrowing (Figure 2.0).

Figure 2.0 Various sites and events which may occur in response to evaporative water loss.



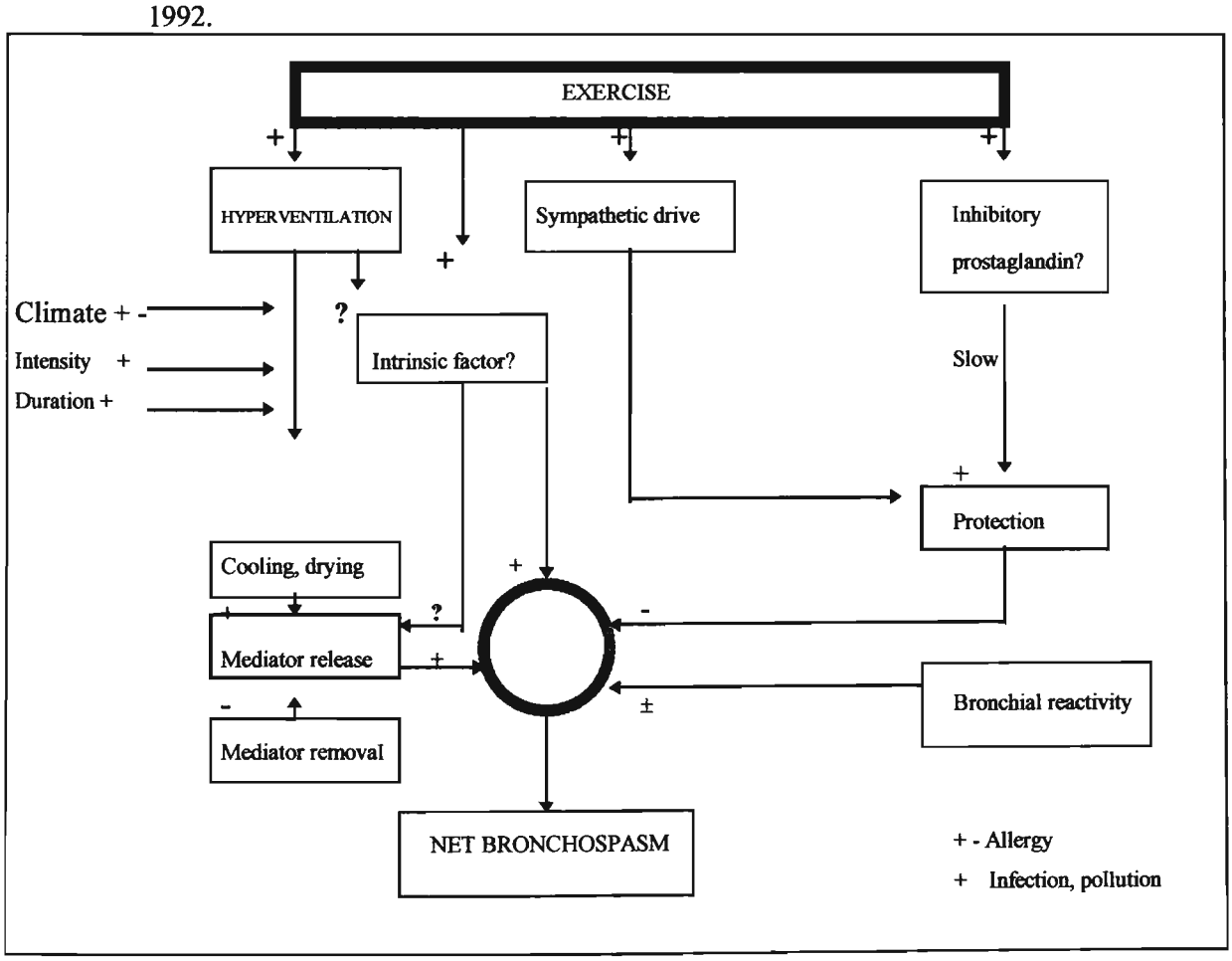
(Anderson, 1985) Schematic diagram of the airways displaying the various sites and events which may occur in response to evaporative water loss.
[NAD = noradrenaline, ∝ = alpha receptor]

Basophils and mast cells release histamine according to Belcher et al. (1988a). Eggleston (1987) demonstrated that increased osmolarity caused mast cells to release histamine. These findings form the basis of the osmotic theory of EIA. Mast cells release sulfidopeptide leukotrienes (C4, D4, E4) which are products of the arachidonic acid cascade. An allergen challenge from the mast cells' reaction may mediate bronchoconstriction by enhancing microvascular permeability and increase nonspecific bronchial hyperresponsiveness (Finnerty et al., 1992). These authors indicated that the release of sulfidopeptide leukotrienes represents a major contribution to exercise-induced bronchoconstriction. Anderson (1988), suggested that mast cells or basophils were involved in EIA by releasing their mediators in response to evaporative water loss and increasing the osmolarity of the perciliary fluid. In contrast to Anderson (1988), Jarjour and Calhoun (1992), demonstrated that the

role of mast cell mediators was to release or increase inflammatory cells in the airspace and that they were not associated with EIA. They tested eleven asthmatics with mild asthma. The research of Jarjour and Calhoun (1992), involved a bronchoalveolar lavage being performed within the hour following an exercise challenge test and the procedure was repeated 24 hours later. From their results they postulated that an exercise challenge in asthmatics was not associated with cellular influx to airspace and that mechanisms other than histamine release by pulmonary mast cells may be responsible for EIA.

Ascertaining the pathways by which the smooth muscle of the airway is affected during and following exercise remains controversial. Two major hypotheses have focussed on the potential stimuli of EIA. The Airway Re-warming Hypothesis and the Heat and Water Hypothesis have both been well supported within the literature. Hendrickson et al. (1994), claimed the controversy intensifies as the data accumulates. His belief was that the cause of EIA was most likely multifactorial, and indicated that a single unifying mechanism was probably non existent. Godfrey (1992), illustrated that the possible mechanisms of EIA included several factors. The interaction and influences of these factors on EIA, are presented in the form of a model (Figure 2.1).

Figure 2.1 Model of exercise-induced and hyperventilation-induced asthma. Adapted from Godfrey, 1992.



Godfrey (1992), proposed that EIA was triggered by an increase in ventilation that was influenced by climatic conditions which produced the cooling and drying of the airways. This environmental-based trigger liberated the mediators which act on the airways resulted in bronchospasm. There appears to be a variety of factors that influence the responsiveness. One of these factors focuses on the level of allergic stimulation. During exercise there is an increase in sympathetic drive which provides a short protection for the asthmatic against bronchoconstriction. In addition to the sympathetic drive there is a slow protection provided by prostaglandins which are released by mediators during exercise causing refractoriness to subsequent exercise. The role of prostaglandins E1 and E2 have been suggested in the development of a tolerance to histamine and are known to relax both vascular and airway smooth muscle and inhibit bronchoconstriction (Margolskee et al., 1988). The prostaglandin-related mechanisms which have been presented further cloud the phenomenon of EIA. In general, the physical stimuli for EIA are not fully understood. The ongoing debate appears to focus on either airways cooling or drying and their respective mechanisms. The purpose of this study however, is not to analyse the validity of the theories supporting the potential pathways linked to EIA, but to examine the responses from exercise in young populations.

Characteristics and Diagnosis of Exercise Induced Asthma

Hough and Dec (1994), outlined the symptoms of EIA which included chest tightness, breathlessness, coughing, and/or wheezing. These authors also indicated that some individuals may experience delayed bronchoconstriction 6-10 hours post exercise (Table 2.0).

Table 2.0: Symptoms of exercise-induced asthma
(Adapted from Hough and Dec, 1994)

- Dyspnoea out of proportion to task
- Post exercise cough
- Poor performance despite level of training
- Chest tightness
- Wheezing
- In children (increased frequency in obese children noted):
  - stomach ache
  - refusal to play
  - chest pain

Morton (1994), defined EIA as "a clinical syndrome characterised by a transient narrowing of the airways following moderate to severe exercise." He stated that in some people, exercise maybe the only stimulus that provokes asthma, and that most asthmatics will have bronchoconstriction provoked by exercise with the degree of post exercise bronchoconstriction related to the severity of the

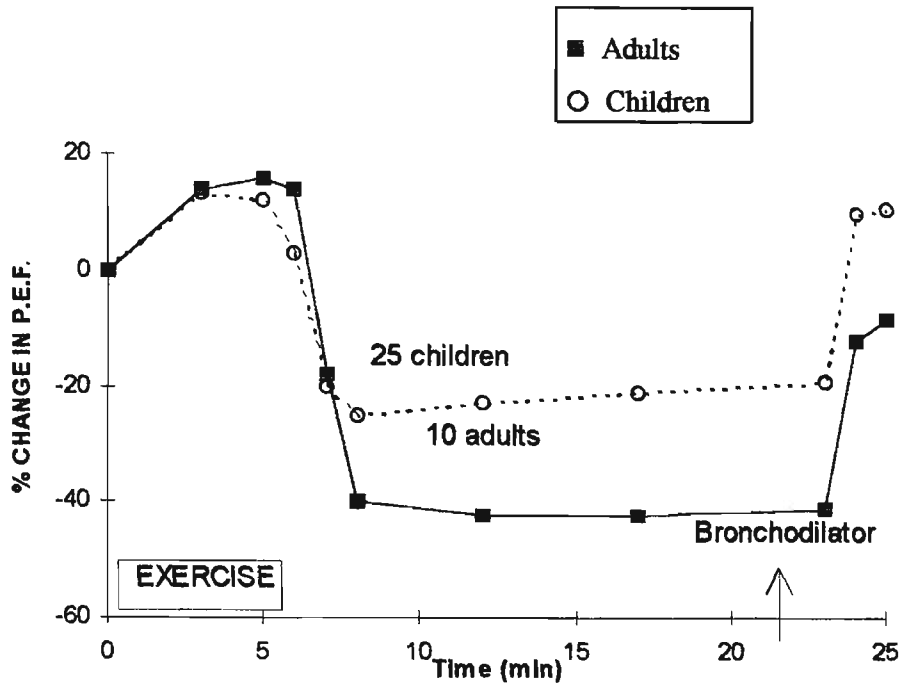
individual's chronic asthma. The symptoms of EIA were described by McFadden and Gilbert (1994), as changes in lung function that were non asthmatic in origin and were developed from untreated pre-existing airflow limitation. Anderson (1985), reported that EIA was characterised by a 10% reduction in PEFR when compared with pre-exercise values in PEFR or FEV_1 post exercise. Similar to Anderson (1985), Morton and Fitch (1993), reported characteristics of EIA as being denoted by a 15% or greater fall in either pre-exercise values in PEFR or FEV_1. They classified the severity of the bronchoconstriction as:

MILD	15-29% fall in FEV_1 or PEFR
MODERATE	30-44% fall in FEV_1 or PEFR
SEVERE	45% or greater fall in FEV_1 or PEFR

It was noted that common symptoms included chest tightness, shortness of breath, fatigue, and coughing. Kattan et al. (1978) investigated the responses of 25 non-asthmatics children between 9 and 17 years of age and 105 asthmatics aged between 7 and 19 years. Each subject performed a 6 minute treadmill exercise challenge test at a slope of 15% with the speed regulated to elicit a heart rate of between 170 and 190 $bts.min^{-1}$. Pre and post lung function tests were performed (FEV_1, PEFR, MMEF and FVC). The PEFR and FEV_1 detected 99% of those asthmatics who had a positive response. The FEV_1 proved to be the more discriminating of the spiromerty measures following an exercise test. Nicklaus et al. (1969), defines EIA as 15 % or greater post-exercise reduction of either the PEFR or FEV_1 on pre-exercise values after standard submaximal exercise stress. Similar values were presented by Fitch (1975) and McFadden and Gilbert (1994). Fitch (1975) diagnosed EIA as a reduction in FEV_1 or PEFR of 15 to 20% following exercise. McFadden and Gilbert (1994) defined the diagnosis of EIA as a recorded fall in the PEFR or FEV_1 of 15% or higher after exercise. The clinical observations of EIA display a reduction of 10% or more in FEV_1 or PEFR post exercise and was acknowledged by Kattan et al. (1978), that these measurements were most effective in discriminating a normal response from an abnormal one. Kattan et al. (1978) further stated that flow volume curves provided minimal additional information in the diagnosis of EIA. Jones et al. (1993) implied that the use of FEV_1 and VC with the use of spirometry yielded important characteristics of airflow obstruction and was usually all that was required for an effective EIA diagnosis.

EIA is a clinical syndrome characterised by transient airflow obstruction typically 5-15 min following exercise according to Mahler (1993). Godfrey (1992) reported that EIA was more severe when the asthmatic reached two thirds of his/her maximum working capacity, with the variation in test duration ranging between 1 to 16 minutes. He found that the severity of EIA increases with exercise duration, and peaked after approximately 6 to 8 minutes' duration. A series of alterations were described to characterise lung function when an asthmatic subject ran for six minutes at a reasonably fast pace and then stopped (Godfrey, 1974).

Figure 2.2 PEF responses of an asthmatic child and adult to 6 minutes of running



Adapted from Godfrey, 1974.

Figure 2.2 displays typical patterns of EIA in children and adults as assessed by measurements of peak expiratory flow rate (PEF). Each point represents the mean of subjects indicated. The magnitude of the post-exercise fall is similar in adults and children (Godfrey, 1974).

Anderson et al. (1972) tested five asthmatic subjects aged between 25-30 years who performed a 6-8 minute steady exercise test on a bicycle ergometer and a treadmill. Arterial blood gases, blood lactates, oxygen consumption, minute ventilation, peak expiratory flow rate, heart rate and duration of work were measured. I t was observed from the four subjects that there was a rise in arterial oxygen tension during exercise. This was followed by a fall after exercise due to hypoxia which was reported to be related to the uneven ventilation from the increased airways obstruction. The blood lactate level was higher during the bicycle test when compared to the treadmill test, but the arterial PCO_2 and pH decreased to similar levels during the test modalities. Ferguson et al. (1969), demonstrated that asthmatic subjects who had dyspnoea following exercise had a decrease of $PaCO_2$ to 23mm Hg compared with 37 mm Hg for non-asthmatic subjects. A decreased arterial carbon dioxide tension has shown to be concomitant with increased lactic acid in moderate and heavy exercise periods. In very

heavy exercise however, only a partial compensation occurs and subsequently, alveolar ventilation may have increased to eliminate carbon dioxide. According to Katz et al. (1975) this may have resulted from metabolic acidosis which is associated with the intensity of the exercise imposed on the subjects.

Anderson (1988), reported that it is not uncommon to observe a drop in PaO_2 of between 60 to 70 mm Hg in asthmatic subjects following exercise. An increase in lung function during exercise may trigger a reversal in the aforementioned hypoxemia-related responses. It was also noted that there were no difference in blood gas tensions or pH between asthmatic and non asthmatics. Numerous investigators have demonstrated that blood gases do not differ from non-asthmatics either during or following exercise (Graff-Lonnevig et al., 1979, 1980, Katz et al., 1971, Paterson et al., 1979, Vassallo et al., 1972,). Katz et al. (1975) reported that subjects who developed EIA, displayed gradient changes of alveolar-arterial oxygen differences and that this would result in ventilation perfusion abnormalities existing at the onset of exercise. These studies highlight the need for a clearer definition of the nature and role of blood gas responses to exercise in asthmatics when compared to non-asthmatics. Further research on ventilatory perfusion rates during exercise in asthmatics may also make a significant contribution to the understanding of factors which limit exercise performance in asthmatics.

Testing Procedures for EIA

In more recent studies Godfrey (1992), mentioned that there is still doubt as to whether running, cycling and other modes of exercise conducted under exact conditions are equally potent stimuli for EIA. The effects of the modes of exercise, duration and intensity used in testing children for EIA have been investigated by several authors (Anderson et al., 1971 and Silverman and Anderson 1972). Silverman and Anderson (1972) conducted a series of exercise tests on asthmatic children and adolescents aged between 5-16 years and non-asthmatic subjects aged between 7-15 years. Exercise tests comprised of running and walking on a treadmill at gradients of 0-20% and speeds of 2.5 -3.5 m.p.h. Each subject performed 5 tests at varying gradients on different days and the following were considered :

1. Effect of workload on EIA.
2. Effect of duration of exercise on EIA.
3. Comparison of running with walking.
4. Reproducibility study.

Their findings demonstrated that running provoked the maximum degree of bronchoconstriction in asthmatic subjects, consisting of 6 to 8 minutes when the gradient of the treadmill was 10-15%. At grades higher than 10-15% and speeds faster than 3.5 m.p.h. no significant increases in bronchoconstriction could be reported. The reproducibility of bronchoconstriction was good when tests were performed in one day or within a week. They proposed however, if several tests were to be performed then they should be conducted on separate days.

According to McFadden and Gilbert (1994), it is immaterial whether the level of ventilation is achieved on a bicycle or treadmill as long as the VO_{2max} is at 60% or greater. The results of research conducted by Bundgaard (1984), support McFadden's and Gilbert's concept. Bundgaard (1984) stated that there was no difference in the ventilatory responses among exercise performances on a bicycle ergometer, treadmill or as a step test, providing the workload is reproducible. The author also emphasised that the exercise should be conducted in a room with a temperature less than 25°C, relative humidity less than 50%, and with a workload which elicits higher than 80-90% $\dot{V}O_2max$ over a period of six minutes. Bundgaard (1984) also advocated that the respiratory readings of PEFR or FEV_1 need to be measured immediately prior to exercise and at 1, 3, 5, 10 and 15 minutes post exercise. For the test to confirm a diagnosis of EIA there needed to be a 20% or greater fall in the baseline readings. Anderson et al. (1975), acknowledged that a 10% reduction in PEFR or FEV_1 has generally been accepted as the upper limit of the normal fall from the baseline measurements following exercise. To establish an accurate diagnosis of EIA Anderson et al. (1984) also believed it was necessary to control a level of ventilation by duration, intensity of exercise and under standardised constant inspired-air conditions. A method for diagnosing EIA was presented by Eggleston (1976) which consisted of a 5 minute treadmill run with increases the subject's heart rate up to 90% of the predicted maximum for their age. The response of the airway was measured frequently for 20 min post exercise. Eggleston (1976) found that the severity of exercise-induced asthma depended on intensity and duration of exercise. He also reported that the changes to the time of the day produced no significant effect on test results. The method described allowed a consistent stress to be applied to subjects from a wide age range. The subjects with greater than 20% change FEV_1 were classified by Eggleston (1976) as having EIA. It has been reported that there are several factors that influence airway response to exercise which should not be overlooked in exercise testing of the asthmatic, these factors are outline in Table 2.1 and have been adopted from Eggleston (1976).

Table 2.1 Factors that require consideration when performing exercise challenge test on asthmatics.

- EIA is best assessed when subjects are not symptomatic.
- Flow rates at rest should be greater than 75% of their predicted for acceptance.
- Ambient conditions should not vary ± 2-3°C , ±10 % relative humidity day to day and < 10mg H_20/L in all tests.
- The measurement of PEFR or FEV_1 is adequate to diagnose EIA.
- Lung function measurements should be taken pre exercise and post exercise at 1, 3, 5, 10 and 15 minutes.
- Withholding medication requires a minimum of 4 hours after an aerosol bronchodilator and 24 hours after oral medication.
- Avoid consuming any drinks or food containing caffeine at least 6 hours prior to testing.
- Avoid exercise at least 3 hours prior to testing.
- Test should be conventional and unskilled type of exercise.
- Heart rate enables the safe adjustments of workload and is a useful means of measuring the intensity of exercise.
- Maintain 60% or greater of predicted MVV for six minutes.

The literature provides a variety of provocation testing procedures to diagnose airway hyperresponsiveness. These procedures involve tests using methacholine, histamine, isocapnic hyperventilation and hyperosmolar saline bronchial provocation tests (Hargreave et al., 1981, Schoeffel et al., 1980, Smith and Anderson, 1986, Smith and Anderson, 1989). It has been demonstrated that Asthma can be diagnosed by implementing either an Isocapnic Hyperventilation or Hyperosmolar Saline provocation test (Phillips, 1985, Smith and Anderson, 1989). The Isocapnic Hyperventilation test provides an alternative method to assess bronchial reactivity, with the advantage of increasing the ventilation precisely by a rotameter. During this procedure subjects breathe dry air containing 4.9% carbon dioxide at 30% of predicted maximum voluntary ventilation (MVV) for 3 minutes, and this is followed by 3 minutes of ventilation at 60% MVV. The subjects are then required to maintain their own MVV for three minutes. Pulmonary function tests are measured immediately before and 3 minutes after each hyperventilation challenge until a positive reduction in lung function is obtained. A minimum of 25-30 L/min^{-1} ventilation is required for eucapnia so that the pre-challenge should exceed 1.5L. This amount however, deems the test inappropriate for small children (Smith and Anderson, 1986, Smith et al., 1988,). Anderson (1986), acknowledged that there was a striking similarity in both the sensitivity and the reactivity of asthmatic subjects to water loss induced by isocapnic hyperventilation and the inhalation of 4.5% saline. Furthermore, according to Makker et al. (1992), hypertonic saline responsiveness established a closer relationship to the severity of EIA symptoms than to the non-specific bronchial hyperresponsiveness measured by histamine or

methacholine reactivity. From the studies conducted by Eggleston et al. (1984), and Smith and Anderson, (1989), it was postulated that hypertonicity provoked bronchoconstriction by causing mediator release from mucosal mast cells or alternatively, caused a disruption of epithelium light junctions by creating an osmotic gradient across the epithelium. The procedure consists of subjects inhaling an aerosol (4.5% sodium chloride) from a ultrasonic nebuliser. The subjects inhaled the aerosol for 30s, and waited 60s before the FEV_1 was measured. If there was a 20% reduction in FEV_1 from the pre-test value, then the test was terminated. If a 20% FEV_1 reduction was not recorded, the provocation test would continue with further exposures at 30s, 60s, 2 minutes, 4 minutes, and 8 minutes, or ceased when a 20% reduction in FEV_1 was recorded (Smith and Anderson 1990). Anderson (1987), reported that in some sensitive patients, airways obstruction can be induced very quickly (ie. within one minute of inhaling the aerosol). The dose which causes a reduction in FEV_1 of 20% (PD_{20}) is used to determine sensitivity to a change in the airways. The advantages of this procedure are that it is a relatively inexpensive test which is safe, and well tolerated. Overall it is reported to be a practical test for stimulating the release of endogenous mediators and identifying current asthma levels. Importantly it also appears to be reproducible in children (Anderson et al., 1995). McFadden and Gilbert (1994), reported that EIA was not difficult to diagnose, however there are certain conditions which could impose intervening influences on a diagnosis if they are not controlled (Table 2.2).

Table 2.2

Factors That Can Confound the Clinical or Laboratory Diagnosis of Exercise-Induced Asthma

False positive diagnosis

- Non-asthmatic airway obstruction, glottic dysfunction, or extra or intrathoracic tracheal narrowing
- Deconditioning
- Exercise symptoms or desaturation due to occult cardiac or pulmonary disease
- Disorders of muscle metabolism

False negative diagnosis

- Insufficient provocation
  - Ventilation too low because of inadequate workload
  - Temperature of inspirate too high
- Medication that may attenuate exercise-induced asthma
  - Selective H_1 antihistamines
  - Calcium-channel blockers
  - α-Adrenergic agonists and antagonists
  - Long-acting methylxanthines and β-adrenergic agonists
    (challenge performed too soon after discontinuation)

(Adapted from McFadden and Gilbert, 1994).

Withholding Medication and the Effects of Anti-Asthmatic Medication

Withholding medication prior to a test may depend on the aims of the test as well as the condition of the subject. Bundgaard (1985) acknowledged that no anti-asthmatic medication should be administered orally within 24 hours prior to the challenge (for example, steroids, theophylline and beta$_2$-agonists including sustained release tablets). He also recommended that there should be no asthmatic medication (for example, steroids, beta$_2$-agonists, sodium cromoglycate, and atropine) inhaled in the four hours prior to the challenge.

The major advances in pharmacological management have provided asthmatics with a satisfactory range of drugs to control asthma, which include sodium cromoglycate, (cromolyn sodium), H1-antagonists, belladonna alkaloids, methyl xanthines, glucocorticoids and beta $_2$-adrenoceptor stimulants. Godfrey (1992), mentioned that the most useful method to protect the patient against EIA is to provide an inhaled selective β_2 sympathomimetic (β_2 agonist) or sodium cromoglycate immediately before exercise. Within the literature there is sound support to indicate that inhaled beta$_2$-agonists drugs and sodium cromoglycate used 10 to 15 minutes prior to exercise are the most common therapies and the more effective therapy before exercise (Baraldi et al., 1994, Green et al., 1992, Tullet et al., 1985). These drugs have been described by Morton et al. (1992), as contributing to an important preventative role in EIA. Table 2.3 presents the common pharmacological agents for asthma and outlining their effects.

Table 2.3 Effects of Common Anti-Asthma Medications on EIA

AGENT	DOSE (PUFFS)	TIMING BEFORE EXERCISE (MIN)	EFFECTIVENESS	HOURS OF PROTECTION
β2 Aerosols				
Salmeterol	2	10-15	+++	10-12
Salbutamol (albuteral)	2	10-15	+++	2.0-2.5
Terbutaline	2	10-15	+++	2.0-2.5
Cromolyn sodium	2	10-15	++	1.5-2.0

Effectiveness is rated as follows: + + +, ablation or substantial reduction in the obstructive response at the midpoint of the stimulus-response curve; marked reduction in obstructive response, (Adapted from McFadden and Gilbert 1994).

No serious side effects appear to occur with multiple use of sodium cromoglycate in EIA, provided that the subject has normal lung function (Albazzaz et al., 1992, Patel and Wall, 1986). Sodium cromoglycate can be administered via a nebuliser, (ampoules, 20mg in 2ml). It is also available in dry powder capsules (20mg Spincaps) or in a metered-dose aerosol form (1mg per puff). Previous reports suggest that the drug has no cardiovascular effects and is particularly useful with children (Morton et al., 1992). According to Rowland (1990), β_2 aerosols provide protection for up to 4 to 6 hours with minimal cardiovascular side effects. This popular agent for prevention of EIA is also effective in the reversal of EIA once it occurs. Morton et al. (1992), and Nickerson (1989) however, reviewed some of the side effects associated with the use of β_2 Aerosols which included skeletal muscle tremor, tachycardia, nervousness, palpitations, and perhaps an occasional significant rise in blood pressure. The inhalation of β_2 agonists for the treatment of EIA symptoms have been recommended as 90% effective by Hough and Dec (1994). For the 10 % of asthmatics for whom EIA is not reversed by a normal dose of β_2 aerosols, an additional dose should be administered by nebulization. It is further recommended that these asthmatics receive oxygen simultaneously. The inability to reverse EIA via a normal dose of β_2 aerosols may be due to the asthmatics' ineffectiveness to inspire deeply from the aerosol bronchodilator during the bronchoconstriction (Anderson 1984). β_2 agonists can be inhaled via different devices which include a metered dose inhaler (MDI), and a MDI attached to a chamber/spacer or a nebuliser. The use of a spacer device has been associated with greater lung deposition of the medication when compared to the use of a metered dose inhaler (Newman et al., 1984). According to Nickerson (1989), portable pumps for aerosolization of β_2 agonists however, provide a more potent and consistent effect than the MDI. The author also cautioned that the expense and inconvenience of using these devices may make them less practical for asthmatics who have occasional symptoms of EIA.

Catecholamines

Adrenaline and noradrenaline are commonly accepted indices of sympathetic activity. They appear to influence cardiocirculatory activity and metabolic reactions as well as playing a major role in adaptations to exercise (Christensen and Galbo, 1983, Galbo et al., 1975). During the period of exercise and shortly after, it is generally accepted that increased levels of circulating catecholamines are responsible for bronchodilation. This bronchodilation is thought to result from the combined effect of endogenously released adrenaline on airway smooth muscle, withdrawal of normal vagal tone, and higher lung volumes (Anderson, 1984). Circulating adrenaline has been associated with several events relating to exercise. These include; eliciting a concentration-dependent bronchodilation, acting as an inhibitor of histamine-induced bronchoconstriction and has also been linked to the inhibition of cholinergic neurotransmission in human airways (Knox et al., 1992, Rhoden et al., 1988). It has been further suggested that continued exercise stress in the form of either continuous low level activity or intermittent work helped to maintain the level of circulating catecholamines. This phenomenon has

subsequently referred to as contributing to the "running through" of the EIA (Godfrey, 1974, Pichurko et al., 1986, Reiff et al., 1989, Schnall and Landau 1980,). According to Barnes (1986), there are three catecholamines present in human plasma. Adrenaline and noradrenaline also appear with dopamine, which is present in very low concentrations and has minimal physiological effect. Noradrenaline is present in the highest concentrations, but when it is found in normal concentration it displays no significant effect on the cardiovascular or metabolic system. Adrenaline has potent metabolic effects that are mediated by β_2 receptors and induces bronchodilation in both asthmatics and non asthmatics. Barnes (1986) suggested that the normally low concentration of adrenaline may act as a defence mechanism against bronchoconstrictor influences such as the inflammatory mediators and vagal reflexes in asthma. Berkin et al. (1988) indicated that circulating adrenaline levels which appear within a normal physiological range have a bronchodilator effect predominantly within the small airways. This was further supported by Warren (1986), who postulated that people afflicted with asthma had circulating adrenaline levels which provided an important defence against bronchoconstriction. On the other hand, noradrenaline has been associated with a lack of responsiveness of the airway and appears to elicit a negligible effect on airway function in either normal or asthmatic subjects. Implicit in these findings is the suggestion that α-adrenoceptors are not important in the regulation of bronchomotor tone (Berkin et al., 1988). The importance of catecholamines in modulating airway tone throughout exercise or following exercise remains unclear. According to Anderson (1988), both α and ß receptors are likely to be stimulated by the catecholamines, and this may delay the onset of bronchoconstriction. Thus, if catecholamines play a significant role in delaying the onset of bronchoconstriction, then they may account for EIA repeatedly occurring primarily after exercise.

The debate about the normal or abnormal responses in catecholamines in people with EIA continues within the literature (Amirav et al., 1994, Barnes, 1986, Belcher et al., 1988a, Dosani et al., 1987, Larsson et al., 1982, Warren et al., 1982). A study conducted by Chyrssanthopoulos et al. (1978), on 7 asthmatic and 9 matched non-asthmatic subjects measured plasma catecholamines at rest, during, and after exercise. They found that exercise-induced bronchospasm occurred in all asthmatic subjects following exercise, with no significant change in the non-asthmatic subjects. Plasma levels of noradrenaline and adrenaline during and after exercise were also similar in both asthmatic and non-asthmatic subjects. Chyrssanthopoulos and co-workers (1978) suggested that the sympathetic response of asthmatics to raised plasma catecholamine levels did not differ from that of non-asthmatic subjects and that the changes in the circulating catecholamines did not play a significant role in the pathogenesis of EIA. Similar findings were reported by Amirav et al. (1994) who tested 13 asthmatic and six non-asthmatic children who performed two bouts of cycle ergometer tests under different air conditions (cold dry air at 20.2°C, with a relative humidity of 0% and the warm humid air at 34.3°C, with 100% relative humidity). These authors showed no differences in the plasma catecholamines concentrations between asthmatics and non-asthmatic subjects in either of the test conditions.

Conversely, Warren et al. (1982) required six asthmatic subjects and six matched non-asthmatic controls to perform a standardised exercise test. The results demonstrated that the plasma adrenaline one minute after exercise, rose over threefold in the controls, while the asthmatic subjects showed no plasma adrenaline increase. They also found that plasma noradrenaline increased to five times the basal concentration in the controls, but was less than half this level in the asthmatic subjects. They postulated that there was a marked abnormality of the sympathoadrenal response to exercise in asthmatic subjects. This was also confirmed in research conducted by Barnes et al. (1981) who tested 7 asthmatics (16.3 years of age) and 6 control subjects (with mean ages of 16.3 and 16.5 years, respectively). These subjects performed a standard six minute treadmill exercise test at a slope of six degrees. They theorised that the plasma levels of cyclic AMP indirectly modulated the effects of catecholamines on beta adrenergic receptors in a variety of tissues and that asthmatics had an attenuated sympathoadrenal response following an exercise stimulus. Barnes et al. (1981) suggested that the reduced sympatho-adrenal response to exercise in asthmatics with EIA, played a role in the pathogenesis of bronchoconstriction by a permissive action on the mast cell.

Section Summary

The differences between asthmatic and non-asthmatic subjects' levels of catecholamines following exercise remain controversial. The variations in the studies previously described, may in part be related to the methods used such as the analysis of catecholamines, and the type, intensity, and duration of the exercise performed.

Refractory Period

Lemanske and Henke (1989), define the refractory period as the time during which repeated exercise under exact conditions induces less than 50% of the initial asthmatic response. They stated however, that the mechanisms of the refractory period following exercise were not able to be precisely identified. Barnes et al. (1981) agreed that the mechanisms for the refractory period were not completely understood, but suggested it may relate to the elevated levels of catecholamines. Various possible mechanisms to explain the refractory period have been discussed within the literature. These include; a desensitisation of smooth muscle to mast cell mediators, the inhibition of mediators effected by increased levels of catecholamines, and a mediator depletion. It has since been hypothesised that mediator depletion was unlikely to contribute significantly towards the refractory period in EIA (Barnes et al., 1986). This was related to the finding that increased circulating catecholamine concentrations decreased very shortly following exercise even though a refractory period may remain for up to four hours. It is unlikely therefore, that increased catecholamines concentrations protect the airways from bronchoconstriction during the refractory period. Catecholamines are not increased during a hyperventilation challenge although this type of challenge is just as effective as exercise and

induces refractoriness. Several authors believe that this phenomenon makes it even more difficult to accept that refractory period relies solely on catecholamine release during exercise (Barnes et al., 1981, Bar-Yishay et al., 1985, Belcher et al., 1988b, Ben-Dov et al., 1983, Carpentiere et al., 1988, Dosani et al., 1987, Eggleston et al., 1986, Edmunds et al., 1978, Hahn et al., 1984b, Lee, 1992, Stearns et al., 1981, Weiler-Ravell et al., 1981). Belcher et al. (1988b) measured circulating mediators and catecholamine concentrations in eight asthmatic subjects who performed two bouts of cycle ergometer exercise which were separated by a one hour rest interval. Serum neutrophil chemotactic activity and plasma histamine were measured as indices of circulating mediators. Belcher and co-workers (1988b) reported a significant increase in neutrophil chemotactic activity and plasma histamine concentrations after both exercise challenges, however, the release of the mediators between the two exercise tests did not differ. The authors therefore concluded that the refractory period in exercise-induced asthma was not caused by mediator depletion (indicated by neutrophil chemotactic activity and histamine measurements), or by protection of the airways through catecholamine release. Godfrey (1992), acknowledged that it is difficult to identify the exact trigger, however he postulated that the pathway leading from this receptor site to the smaller airways could be humoral, neurological or a combination of both mechanisms.

Anaerobic Metabolism

Exercise of short duration consisting of high intensity such as sprinting 50 meters, long jumping or performing a weightlifting manoeuvre such as a "power clean" require an immediate and rapid supply of energy which is supplied exclusively from the high energy phosphates known as adenosine triphosphate (ATP) and creatine phosphate (CP). Both these phosphates are stored within the muscle (Saltin, 1973). This most rapid method of producing ATP involves the donation of phosphate group and its bond energy from CP to adenosine diphosphate (ADP) to form ATP.

$$CP + ADP \underset{\text{Creatine kinase}}{\rightleftharpoons} ATP + C$$

Creatine kinase is the enzyme that catalyses the reaction, as the ATP is broken down to ADP + inorganic phosphate (Pi) at the onset of exercise and ATP is reformed via the CP reaction (Bessman and Carpender, 1985). Muscle stores of the high energy phosphagens ATP and CP, are limited and the total intramuscular reserve of phosphagen is small. Consequently both ATP and CP stores could be exhausted in as little as 2 seconds. Phosphagen reserves are not likely to sustain longer than 10 seconds of high intensity effort. If this did occur the high energy phosphate bonds would need to be regenerated from other energy sources within the muscle ie. by either aerobic metabolism or anaerobic glycolysis. Anaerobic glycolysis is an oxygen independent energy source which is derived from the breakdown of intramuscular glycogen stores. These stores can be supplemented by hepatic gluconeogenesis (Shepherd, 1992). More specifically anaerobic glycolysis is characterised by the breakdown of glucose or glycogen to form two molecules of pyruvic acid or lactic acid. It plays an

important role in regenerating large amounts of ATP per unit of time. Its major limiting factor is however, a decrease of intracellular pH within the active muscle fibres (Saltin, 1973). Sahlin et al. (1976) reported that at a pH of 6.3 the key rate limiting enzymes such as phosphofructokinase (PFK) are inhibited and glycolysis can no longer be sustained. Hermansen (1969), suggested that there are a variety of contributing factors which limit anaerobic work. He outlined these factors as: the initial levels of muscle glycogen, the rate of production of ATP in the muscle, the ability to tolerate a high level of lactic acid, and the ability to tolerate low intracellular pH. Other investigators however, have found that there may be additional factors which may limit anaerobic work. These factors include; the training status of the subject (resulting in an increased buffering capacity and glycolytic potential), the distribution of skeletal muscle fibre types (given the greater glycolytic potential of the type II or fast twitch fibres), and the ability to clear lactate from the active muscle (Bouchard et al., 1982, Parkhouse and McKenzie, 1984, Sahlin and Henriksson, 1984, Saltin, 1973).

There are two notable advantages of anaerobic glycolysis as a means of activating muscle mass. These advantages are found in the characteristics of functioning without oxygen and providing a high power output. These characteristics are considerably beneficial when there are limitations on the rate at which oxygen can be aerobically processed or when the power output demands are high. The power output of the working muscle during anaerobic glycolysis can only be surpassed by phosphagen hydrolysis or by direct ATP hydrolysis (Hochachka et al., 1983). The understanding of the role of anaerobic glycolysis was advanced by the research of Stainsby and Eitzman (1986) who demonstrated that during anaerobic glycolysis the production of lactate is known to supplement aerobic metabolism as a means of making up any energetic shortfall.

Medbø et al. (1988) ascertained that brief high intensity exercise is unaffected throughout hypoxic conditions because there is stronger reliance on anaerobic metabolism. The power output can be maintained despite a diminished aerobic energy yield, however the maintenance of performance cannot be sustained. A study performed by Linnarson et al. (1974) required the subjects to perform a maximal cycle ergometer test under the influence of hypoxic, normoxic and hyperoxic conditions for the duration of 3.4 - 4.8 minutes. They showed that in submaximal exercise; oxygen deficit, phosphagen depletion, and muscle lactate accumulation (which are independent of oxygen partial pressures and are indicators of anaerobic energy yield), were inversely related to inspired oxygen partial pressure. Thus Linnarson and co-workers (1974) reported a greater anaerobic energy release in hypoxic environmental conditions under submaximal exercise workloads.

Hochachka et al. (1982) found that when animals lived at high altitude for an extended period of time, they demonstrated an upward scaling of oxidative capacity. This was indicated by an increase in absolute activities of citrate synthase (CS) and hydroxyaclCoA dehdrogenase (HOAD). The authors also made observations of a downward scaling of anaerobic/aerobic metabolic potentials of the heart which were indicated by low ratios of lactate dehydrogenase (LDH) to CS and LDH to HOAD, but

high ratios of pyruvate kinase to LDH. From their findings Hochachka et al. (1982) suggested that animals of long term adaptation to high altitude had an increased rate at which oxygen and substrates could be fluxed through the system. This flux capacity was attributed to an increasing level of enzymatic activities and mitochondrial abundance. According to Hochachka et al. (1983) under normal conditions the ion and electrical potentials cannot be sustained because of insufficient energy and high membrane permeabilities. These are believed to cause the metabolic and membrane functions to be coupled. They found that hypoxia-tolerant animals were able to resolve these problems via a number of biochemical and physiological mechanisms. These mechanisms included:

a) "Metabolic arrest" which was achieved by means of a reversed or negative "Pasteur effect" (reduced or unchanging glycolytic flux during limited O_2 availability). This meant that coupling of metabolic and membrane function was achievable, in spite of the lower energy turnover rates.

b) "Membrane stabilisation", which was achieved by maintaining membranes of low permeability (probably via reduced densities of ion-specific channels).

These proposed functions were thus suggested to potentially extend the tolerance to hypoxia. It has been previously reported that asthmatics displayed lower plasma lactate levels following supramaximal intensities compared with non-asthmatics (Karila et al., 1992). The possible mechanism for an attenuated anaerobic index could be found in the postulation that asthmatics have developed similar adaptations to those observed in animals living at high altitude. This implies that asthmatics could subsequently be more sensitive to hypoxic conditions. It has been reported by Saltin (1987) however, that because high altitude, reduces the availability of oxygen, it may be advantageous in the training of the anaerobic energy yield as it may favour glycolysis and lactate formation. Thus the hypothesis of Karila and co-workers (1992) may require further research to eliminate the possibilities raised by Saltin (1987).

Anaerobic Characteristics of Children

Gollnick et al. (1973), and Eriksson et al. (1973) established that the glycolytic rate limiting enzyme (PFK) had a lower activity in children, when compared to adults. These researchers subsequently predicted that children would have a lower anaerobic capacity. It was suggested that the rate of breakdown of ATP and CP during exercise is similar in children and adults in relation to the oxygen deficit, however the values were reported to be higher if the children were trained (Macek, 1986). Other early studies demonstrated that maximal anaerobic power was significantly lower in children compared to adolescents and adults (Margaria et al., 1966). In support of this finding, Bar-Or (1983) and Inbar and Bar-Or (1986), showed that poorer anaerobic performances in the Wingate tests of children when compared to adults could be associated with a number of factors.

They postulated some of these factors to include; lower maximal lactate concentrations within muscle and blood, lower levels of acidosis at all-out exercise, and lower rates of glycolysis. Some of the early research conducted by Krotkiewski et al. (1980) demonstrated that lactate production is influenced by the levels of circulating testosterone. In a discussion of this investigation Bar-Or (1983) suggested that it may be premature to state that the differences in male hormone activity between boys and men may relate to the differences observed in the rate of glycolysis. The Accumulated Oxygen Deficit (AOD) is a more recent method of assessing anaerobic performance than the Wingate Anaerobic test. While the method is described in more detail elsewhere in this review of literature, one of the major differences between the two tests lies in the fact that the AOD test is performed at 'supramaximal' intensities to exhaustion rather than the fixed all out period of 30 or 60 seconds which is imposed by the Wingate Anaerobic Test. Carlson and Naughton (1993), demonstrated that children also have an inferior AOD in absolute and relative terms when compared to adolescents and adults. Thus it appears that it has been well established within the literature that children have limited anaerobic characteristics compared to adults (Table 2.4). There are however, few investigations that have examined the anaerobic characteristics of asthmatic children compared to non asthmatic children.

Table 2.4 Studies involving Anaerobic Characteristics of Children and Adults

Authors & Year	Group	Nature of the Study	Major Findings
Astrand, 1952	68 boy & girls	Physical Work Capacity in relation to age and sex	The peak recovery lactate for children was on average 9mM significantly lower than adults.
Margaria, et al. 1966	children, adolescents and adults	Measuring anaerobic power during a stair climb test	Children had a lower anaerobic power compared to adolescents and adults showing that there is a gradual increase with age, reaching max at 20-30 years.
Eriksson, 1972	11-13 year old boys	Examining the oxygen supply and muscle metabolism in an all-out test	Lower muscle lactate concentrations in the boys (about 10 $mM.kg^{-1}$ wet muscle) than usually noticed in older subjects (20 mM or higher). Lower PFK in boys compared to adults.
Eriksson, 1973	11-13 year old boys	Effects of training on the skeletal muscle metabolism	Following the training, children had a lower levels of PFK and blood lactate compared to adults.
Bar-Or, 1983	Children, Adolescents and Adults	Measuring the anaerobic processes using the Wingate test.	Increases with chronological age were found in: absolute mean power, mean power relative to body weight, absolute peak power and peak power relative to body weight.
Berg, & Keul 1988	Children 4-18 years	Measured the muscle enzyme activity level for aerobic and anaerobic energy sources	There was an increase in PFK with age. The ratio of the enzymatic activities of fumarase to pyruvate kinase were 100% higher compared to adults, Children have a greater potential for aerobic than anaerobic metabolism than adults.
Mero, 1988	Children 10-13 years	Examining the relationship between blood lactate to muscle fibre area and serum testosterone following a high intensity bicycle exercise (15 & 60sec.)	The children's blood lactate levels were positively related to muscle fibre area type II% and serum testosterone levels. He postulated that lactate levels were related to maturation, training status and genetic endowment.
Karila et al. 1992	14 asthmatic & 14 non asthmatic children	To examine the anaerobic fitness and lactate levels of asthmatics following a maximal exercise test and a high velocity test performed on a cycle ergometer.	The asthmatic children displayed a lower, lactate level during the high velocity test and a higher level of lactate during the maximal exercise test. They found asthmatics have a lower aerobic and anaerobic physical fitness.
Carlson & Naughton, 1993	18 active children	To investigate the MAOD technique as a measure of anaerobic capacity.	The oxygen deficits appeared to be inferior to those in adults from other studies.

Various Types of Exercise Responses with Asthmatics

Several investigations have attempted to identify which type of exercise is the most potent stimulus for EIA. Results of some studies suggest that running is the most asthmogenic form of exercise (Anderson et al., 1971, Fisher et al 1970, Fitch and Morton, 1971, Godfrey 1974,). When ventilation is standardised among different types of exercise there is no difference in EIA following running, cycling, walking and swimming (Deal et al., 1980, Kilham et al., 1979, Kivity and Souhrada 1980, Tweeddale et al., 1981). Bundgaard et al. (1981), tested 11 adult asthmatics' running performance on a treadmill and compared these results with an isocapnic hyperventilation test. The ventilation, temperature of the inspired air, and the relative humidity were kept constant during the tests. The decrease in peak expiratory flow following the treadmill-running was similar to the decrease in peak expiratory flow following isocapnic hyperventilation. Bundgaard and co-workers (1981), postulated that ventilation was of more importance for the decrease in pulmonary function after exercise, than the work load. The purpose of this section of the review of literature however, is not to challenge the types of exercise that are most asthmogenic but to explore the responses and performances from shorter duration exercises of high intensity.

Short-Term High Intensity Intermittent Exercise

It has been well supported within the literature that continuous exercise is much more asthmogenic than intermittent exercise (Eggleston et al., 1976, Edmunds et al., 1978, Godfrey 1975, Jones et al., 1963, McKenzie et al., 1994, Morton et al., 1982, Wilson and Evans 1981). Minimal attempts have been made to examine the response to shorter durations of exercise in asthmatics and the effect on EIA of brief high intensity exercise. Jones et al. (1962), showed that a minimum amount of work or (threshold) needed to be exceeded before EIA occurred. This was supported by Silverman and Anderson (1972) who observed that asthmatics demonstrated a mild degree of bronchoconstriction following submaximal treadmill exercise of only 2 minutes duration. From their findings they indicated that certain combinations of severity and duration of exercise should achieve this threshold. Morton et al, (1983) recruited 14 healthy asthmatics (mean age of 23.6 years) who participated in a $\dot{V}O_2$max and five separate tests involving running on a treadmill at 75% of $\dot{V}O_2$max for 2, 8, 16, 24 and 32 minutes. The results showed significant bronchospasm following all exercise tests from 2 to 32 minutes. The severity and length of the bronchoconstriction was however, less following the exercise bout for two minutes when compared to tests of longer duration. More specifically, the other exercise tests which ranged from 8 to 32 minutes displayed no difference in either incidence or severity of EIA. A similar study was conducted by Godfrey et al. (1974) which involved asthmatic children running at different speeds and slopes of maximal efforts for 1.5, 3, or 6 minutes. The shortest of these maximal sustained efforts would have had a major anaerobic contribution. The results of the 1.5 minute test demonstrated substantially lower levels of EIA developed when compared with the results of the 3 and

6 minute tests. Godfrey et al. (1974) concluded that the severity of EIA appeared to depend strongly on the total work completed, and that the nature of the protocol used was unimportant as long as the exercise was running.

Schnall and Landau (1980) conducted a study using 6 subjects who had been diagnosed with EIA. The subjects ages ranged from 12 to 31 years. Testing involved a series of 7 x 30 second sprints with 2.5 minutes recovery between sprints. They found that repeated short sprints minimised the bronchoconstricting effect of subsequent exercise. Schnall and Landau (1980) postulated that this response may have been related to an increase in circulating catecholamines or altered vagal-sympathetic balance. The sprint efforts in this study were only performed at a work intensity 120-130% above that used in the normal running test, and a work:rest ratio of 1:5 was used. The workload intensities were not applicable to the natural play activity patterns of children and demands of common Australian team sports; football, netball, cricket, hockey, squash, tennis, basketball, soccer and softball which involve intermittent efforts of high intensity and only a few seconds duration which are often supramaximal in terms of the individual's maximum aerobic power (Naughton and Carlson, 1990). There appears to be little evidence of exercise protocols which have attempted to match the laboratory-based testing with the spontaneous nature of children's play.

Similar findings to the Schnall and Landau (1980) study described above were observed in a study by de Bisschop et al. (1992) who tested 30 asthmatic children (mean age of 12 years). The subjects were required to perform a 7 minute run and two series of five short runs lasting 26 seconds, separated by five minutes of rest at a speed equalling 120% of the 7 minute run. The seven minute run was found to be more asthmogenic than the shorter tests and the series of short runs was described as being well tolerated and resulted in reduced EIA in the young asthmatics.

Morton et al. (1982) investigated the effects of intermittent and continuous exercise on 27 asthmatics whose ages ranged from 12 -35 years. The subjects performed a continuous treadmill run for six minutes at 85 % of the predicted maximal heart rate. In addition to the continuous test, four intermittent exercise protocols were imposed:

1. intermittent running -3 minutes work. 5 minutes rest, 3 minutes work at same workload as the continuous.
2. intermittent running 36 x 10 seconds work with 30 seconds rest at the same workload as the continuous.
3. intermittent running 20 x 10 seconds work with 30 seconds rest at 175% of workload used in the continuous test.
4. intermittent running 10 x 20 seconds work with 60 seconds rest at 175% of workload used in the continuous test.

FEV_1 measurements were conducted pre and post exercise tests. The total work accomplished in each test was equivalent to the six minute continuous running test. The continuous exercise protocol showed the greatest decrement in pulmonary function when compared with the intermittent work bouts. When the work was performed intermittently, running 36 x 10 seconds work with 30 seconds rest at the same workload as the continuous caused less airway obstruction compared with the other intermittent protocols. The intermittent work periods were 10 and 20 seconds and were applied using a 1:3 work to rest ratio. Hence, the overall times of the intermittent work regimes were all more than twice as long as the 6 minute continuous test. If it is accepted that a major factor in EIA is the influence of the drying of the mucous membranes in the airways by a bulk flux of drying air, then it can be speculated that the overall respiratory stimulus in the intermittent tests was only just over that experienced from the continuous exercise test. It was not surprising therefore, that the EIA response was attenuated by intermittent exercise. The two previous studies which examined responses to bouts of short term exercise did not examine the ventilation as an indicator of bronchial cooling. These previous exercise tests were also not true anaerobic high intensity tests (110-130% $\dot{V}O_2max$) and involved short durations of less than a minute with the work to rest ratios of less than 1:3. Comparisons of results were subsequently difficult. These studies also indicated the literature to date is inadequate in its explanations of high intensity exercise and EIA in young populations.

Inbar et al. (1981) conducted a study on 10 asthmatics (mean age of 32 years) in which they examined the effects of a short-exhaustive exercise. These tests were conducted on a treadmill for a duration of between 40 to 50 seconds. An additional longer-term submaximal running test was also conducted at a workload intensity which elicited a heart rate of 85% age predicted maximal heart rate. Following these tests Inbar and co-workers (1981) measured forced vital capacity (FVC), forced expiratory volume at 1 second (FEV_1), mid-maximal expiratory flow (MMEF), airway resistance (R_{aw}), thoracic gas volume (TGV), specific conductance (Sg_{aw}) and V_E BTPS. Arterial blood samples were measured for pH and lactic acid concentrations. The short durations of the supramaximal treadmill running tests which were conducted for less than 1 minute, caused a drastic fall in MMEF but no significant changes in FEV_1 (6%) or R_{aw}. It was suggested that the unequal ventilatory responses from the two exercise modes may have been responsible for a greater respiratory heat loss during the long-submaximal exercise. The authors believed that this would lead to more significant obstruction of the large airways, following continuous exercise stresses when compared to results from shorter term high intensity tests. The short-exhaustive exercise performed may also serve as a simple and accurate tool for detecting small airway obstruction as measured by the MMEF. The blood lactate was significantly higher and the pH significantly lower following the short exercise bout compared with the longer submaximal test, suggesting that the pH, lactate and hypocapnia were not primary triggers for EIA. Inbar and co-workers, subsequently suggested that these three aforementioned variables may have been secondary causes of increased ventilation. In their study the treadmill speed was set at 8 kph for all subjects with the slope adjusted to cause a state of exhaustion within 40 -50 seconds (mean power

output 1000 ± 70kgm.min^{-1}). Unfortunately, Inbar et al. (1981) did not provide a rationale for the prescribed workload. They further omitted to describe the intensity at which supramaximal exercise was performed. It has been demonstrated that exercise durations of less than two minutes usually fail to cause large airway obstruction but in asthmatic subjects bronchodilation can result from shorter exercise bouts (de Bisschop et al., 1992, Godfrey 1975, Jones et al., 1962, Silverman et al., 1972, Schnall & Landau 1980). There is however, no evidence of studies examining a bronchoprovocation response to equivalent potent high intensity intermittent work.

Anaerobic Testing

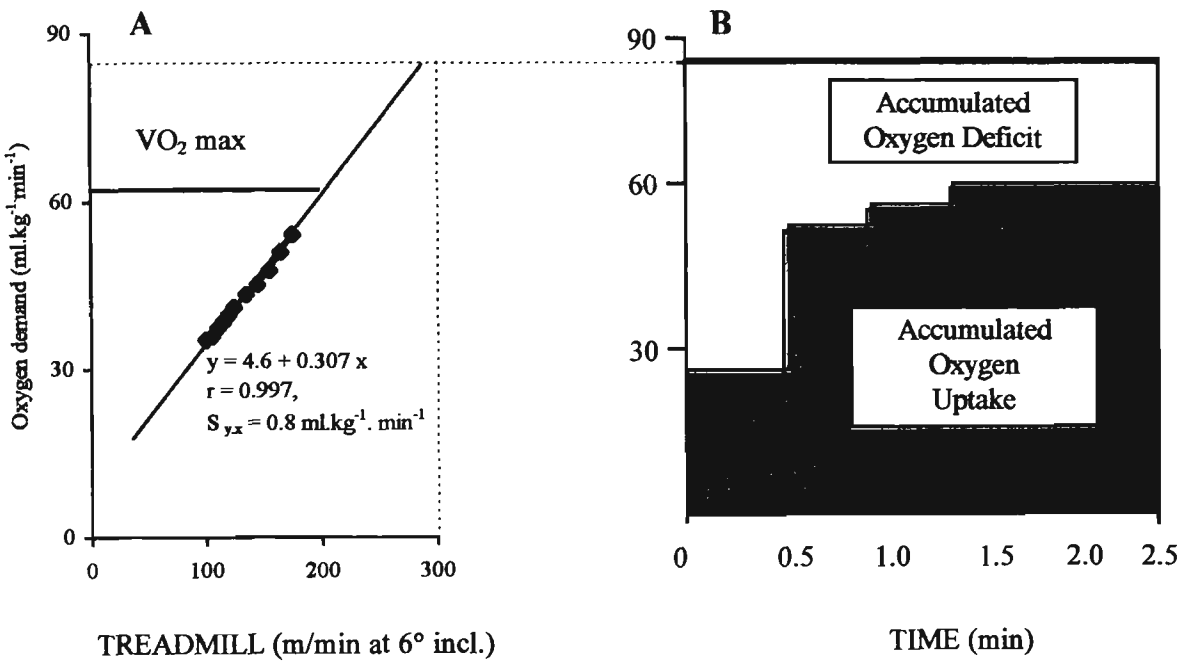
Anaerobic testing has been categorised into two types of tests: anaerobic power tests and anaerobic capacity tests (Vandewalle et al., 1987). Sargeant (1989) advocated the use of anaerobic power tests. According to Sargeant (1989), muscular power from short duration physical activity, derives from a variety of factors including the proportionate contribution of energy pathways, efficiency of energy transformation, muscle size and structure, and the patterns of recruitment and coordination. Due to the invasive procedures necessary for the most accurate estimate of the aforementioned internally-based factors, a variety of tests have been designed to approximate the quality of internal muscle metabolism and concomitantly measure the external power produced in a standardised test. These anaerobic power tests include vertical jumps, stair climbs, force-velocity curves and all-out cycling tests. A test that is frequently used to assess the anaerobic performances is the Wingate Anaerobic Test (WAnT). It was designed at the Wingate Institute in Israel to assess the ability of a specific muscle group to perform short supramaximal exercise. The limiting factor in the performance on a WAnT is the ability to convert anaerobic chemical energy to mechanical energy under high intensity exercise demands (Bar-Or, 1983). The test was originally performed on either a cycle ergometer or arm cranking ergometer for 30 seconds at maximal speed against a constant resistance. The resistance is predetermined to yield supramaximal power outputs (equivalent to two to four times the maximal aerobic power). Performance measures from this test include peak power (the highest mechanical power produced during any 3 to 5 second period), mean power (the average power sustained throughout the test), and fatigue index or the rate of fatigue which is determined by the power decrement during the test, expressed as a percentage of peak power (Bar-Or, 1987). The resistance for each subject during a WAnT is critical to the power output.

Numerous investigations have focussed on determining an optimal resistance setting for the WAnT. There have been suggestions that large differences exist in relation to optimal resistance for peak and mean power outputs from the WAnT (Bar-Or, 1987, Dotan & Bar-Or, 1983, Evans & Quinney, 1981, Naughton and Carlson, 1995, Patton et al., 1985). The optimisation of resistance setting is dependent on a variety of factors such as age, sex, body composition, cycling ability, test duration, test intensity, and training status. Despite the abundance of investigations determining an optimal resistance, the issue remains unresolved. The original resistance for the cycle ergometer was 0.075 kg.kg.BM^{-1}, and

was initially performed on 13-14 year old untrained subjects (Ayalon et al., 1974). A review of anaerobic testing written by Vandewalle et al. (1987), suggested that the optimal resistances for the 30 second WAnT appeared to be 0.095 kg.kg.BM^{-1}, 0.086 kg.kg.BM^{-1}, and 0.075 kg.kg.BM^{-1} for adult males, adult females and children, respectively. Previous studies have shown that the WAnT is reproducible with children and under different climatic conditions (Bar-Or, 1987, Dotan & Bar-Or, 1983), and has a similar coefficient of correlation to those documented for adults (Naughton et al., 1992). The WAnT is a popular test for anaerobic assessment in laboratories and appears to provide valuable performance based information. Kavanagh and Jacobs, (1987), however argued that the work scores include aerobic energy sources which may contribute as much as 9-19% of the total energy required. For these short-term anaerobic tests therefore there is a substantial contribution from aerobic energy sources. This however may depend on mechanical efficiency. It has also been shown that considerable amounts of anaerobic energy supplies still remain following short term "anaerobic" power tests lasting 30 seconds or less such as the WAnT (Saltin, 1990). Medbø (1991), described exercise as high intensity when it was conducted at an intensity above the limit set by the maximal O_2 uptake, and he refers to this as "supramaximal" exercise. He believed that the most valid tests of anaerobic energy contribution focus on a performance to exhaustion under high intensity exercise conditions. He further reported that the most precise quantifiable measures of anaerobic capacity would require the potential to separate and define anaerobic and aerobic energy production.

Medbø et al. (1988), defined the anaerobic capacity as the maximum amount of ATP which can be supplied by the anaerobic energy system under high intensity exercise demands performed to exhaustion. He described a method known as the "maximal" accumulated oxygen deficit (AOD) as a valid estimate of the anaerobic capacity. The method relies on obtaining steady state O_2 uptake from submaximal workloads (Figure 2.3), and uses these data to calculate a least squares linear regression from the workload - O_2 uptake relationship. Extrapolations are also made from the linear regression equation to predict supramaximal intensities (intensities with a rate of energy release exceeding the maximal O_2 uptake). The O_2 demand for supramaximal intensities is calculated from known values obtained in peak maximal aerobic power tests. The accumulated O_2 deficit for a given exercise bout at a constant intensity is then equal to the difference between the predicted O_2 demand and the actual O_2 uptake during the exercise bout to fatigue (Medbø, et al., 1988).

Figure 2.3 Principles for determining O_2 deficit



Slope of the regression of the steady-state oxygen uptake on treadmill speed at 6° inclination.

A: relationship between exercise intensity (treadmill speed) and O_2 demand.

B: accumulated O_2 deficit is calculated as difference between accumulated O_2 demand and accumulated O_2 uptake of exercise. Adapted from Medbø et al. 1988.

This method has been described as a non invasive method to estimate the anaerobic capacity (Gastin and Lawson, 1994, Karlson and Saltin, 1970, Linnarsson et al., 1974, Medbø and Burgers, 1990, Medbø et al., 1988, Medbø and Tabata, 1987). The underlying assumptions of the method however, have been challenged by various authors for not being an accurate measure of anaerobic production. The main concern centres on difficulties in accepting the validity of the assumption that mechanical efficiency can be extrapolated from submaximal exercise to predict energy demands during supramaximal exercise. Several authors believe predicted costs for supramaximal exercise are likely to be underestimated from this method and would result in a lower "true" anaerobic capacity (Bangsbo et al., 1993, Olesen, 1992, Saltin, 1987, 1990, Vandewalle et al., 1987). The AOD method has not been widely examined in children and there are no published studies where this method has been used on asthmatic populations. A study of AOD responses of 18 children with an average age of 10.6 years demonstrated the performances of these children were inferior to those of adults reported in other

studies (Carlson and Naughton 1993). The accumulated oxygen deficit values ranged from 31.8 to 40.4. $ml \cdot kg^{-1}$ in children and were compared with the values from the previous studies cited on adults which ranged from 42 to 81 $ml \cdot kg^{-1}$. Similar findings in children were reported by Eriksson et al. (1973) who reported accumulated oxygen deficit values of 35 $ml \cdot kg^{-1}$ in 11 to 12 year old boys. Carlson and Naughton (1993) concluded that the AOD method is a noninvasive, and challenging protocol for determining the anaerobic performances which appeared suitable for use in younger populations. The authors however, cautioned the need for further validation of the protocol and type of equipment required for optimal performances when testing for AOD values in children and adolescents. Scott et al. (1991) stated that "direct measurements of anaerobic capacity are lacking and thus no "gold standard" exists for direct validation." There has however, been sound evidence to support the AOD test validity and it appears to be sensitive enough to detect anaerobic differences without invasive procedures. This characteristic encourages its usefulness within paediatric populations.

Maturational Indices

A study by Falgairette et al (1991), investigated the effects of growth and development on the bio-energetic characteristics of males aged 6 - 15 years. They found that growth and maturation together play an important role in the development of anaerobic metabolism. Astrand and Rodahl (1986), stated that chronological age is not a very good reference point when analysing performance data, particularly in the case of children and adolescents. Tanner (1962) conducted extensive research on sexual maturation in males (pubic hair, development of scrotum, testis, and penis) and females (breasts and menarche) and described the sequential development in terms of stages. It was further demonstrated that changes in hormone concentrations are related to chronological age and the sexual maturational stages formalised by Tanner (1962). The availability of much improved endocrine assay techniques has focused attention upon hormones as major determinants of human growth and development. For example when serum hormone concentrations are graphed against pubertal stage a positive relationship exits between the endocrine and the clinical phenomena of puberty (Winter 1978). The measurement of steroid hormone concentrations in saliva is a useful method for assessing endocrine function in 'growing' populations (Walker et al., 1980). Tames and Swift (1983) tested the salivary testosterone levels in 1000 male school children between 9 and 17 years demonstrated the level to be uniformly low in 9 year olds, and linearly related to age (Table 2.5).

Table 2.5 Salivary testosterone concentrations of schoolboys ranging between 9 and 17 years old

Age (yr) n	Conc. (pmol/l)
9 (73)	76 ± 42
10 (74)	82 ± 29
11 (63)	122 ± 56
12 (90)	165 ± 86
13 (226)	285 ± 230
14 (108)	347 ± 122
15 (161)	368 ± 172
16 (184)	369 ± 156
17 (68)	390 ± 98

M± SD (Adapted from Tames and Swift, 1983)

Riad-Fahmy et al. (1982), reported that salivary sampling regimes have the advantage of being an easily collected, noninvasive, and stress free technique. The measurement of salivary testosterone is a useful index of maturation status in exercise testing with paediatric populations, particularly when anaerobic metabolism has been shown to change with puberty (Eriksson et al., 1973, Falgairette et al., 1990 and 1991, Paterson et al., 1986).

Rating of Perceived Exertion

Ratings of perceived exertion (RPE) have been described as a useful clinical tool during exercise stress testing which assist researchers to gain an understanding of a subject's level of perceived stress (Noble 1982). Killian (1987) demonstrated a strong correlation between sensations of dyspnea and RPE in

adults with asthma and individuals with normal lung function values. In support to this study, Yorio et al. (1992), found breathlessness was a strong and independent predictor of ventilatory stress in young women with mild asthma at exercise intensities approximating 75% and 88% $\dot{V}O_2$ max test. Mahon and Marsh (1992), tested 30 children (mean age of 10.4 years) who performed two graded running tests for the assessment of ventilatory threshold (VT) and $\dot{V}O_2$ max. They reported that the reliability of RPE at ventilatory threshold was consistent with previous studies which have examined RPE reliability in children during exercise at a set intensity. They noted however, large inter-individual variations in the RPE at VT. The authors (1992) believed that this was due to the variation in VT between subjects. From this finding Mahon and Marsh (1992) concluded that RPE should be used with caution when assessing exercise intensity based on perception of effort in this age group. RPE has been used widely as an indicator of perceived stress, but exact physiological mechanisms by which the perception of effort is determined has yet to be elucidated (Prusaczyk et al., 1992).

Conclusion

This review of literature began by discussing the possible mechanisms for EIA displaying controversy among prominent researchers. The aim of the review of literature however, was not to identify and accept specific theory but to present possible outcomes and concepts which may be leading to this phenomena of EIA. It was further evident that the literature has not displayed a wealth of research focussing on the anaerobic metabolism and characteristics of the asthmatics during exercise. The characteristics and diagnosis of EIA have been well established. In contrast to this, there appears to be relatively fewer studies examining the asthmatic potential of the typical characteristics of children's natural play activities. These activities comprise of spontaneous play patterns incorporating anaerobic characteristics. The presented literature therefore, undoubtedly justifies a need to explore the responses that occur with short term exercise in children with EIA. and to examine whether the responses differ between asthmatic and non-asthmatic young populations.

Chapter Three

Methods

Chapter Three

Methods

This chapter describes the subjects, and general data collection procedures adopted in this research. Within this research there were several procedures common to more than one study. It is these procedures which have been described in this chapter. More specific details of methods designed to meet the particular goals of each study will be outlined in the appropriate chapters.

Subjects

A total of 58 subjects participated in this research, with 50 males and 8 females. Their ages varied between 9 and 17 years. All children were volunteers from suburban Primary and Secondary schools. These volunteers were also regularly engaged in physical activity which was denoted by consistent participation in Physical Education classes and attendance in at least two hours of organised sporting activities outside of school hours. The subjects in all three studies displayed positive results from the provocation tests ranging from mild to moderate classification as described on page 19, Chapter Two (Morton and Fitch, 1993).

Table 3.0 Descriptive characteristics of the subjects used in the three studies.

Study	n	Age (yr)	Mass (kg)	Height (cm)	BMI ($kg.cm^2$)	Tanner Scale	VO_2 Peak ($ml.kg^{-1}min^{-1}$)
One	20	9-12	25-51	125-153	13.31 - 23.37	1	43-71
asthmatics	10	10-12	25-51	132-148	13.31 - 23.37	1	46-71
non-asthmatics	10	9-11	25-48	125-153	16.19 - 21.51	1	43-63
Two	18	10-11	28-52	133-157	15.19 - 26.39	1-2	50-66
asthmatics	10	10-11	28-44	133-157	15.70 - 20.74	1-2	50-66
non-asthmatics	8	9-11	32-52	135-151	15.19 - 26.39	1-2	42-64
Three	21	13-16	42-80	149-175	16.58 - 27.00	3-5	43-62
asthmatics	10	13-16	42-80	149-175	16.62 - 27.00	3-5	43-62
non-asthmatics	11	13-15	45-73	160-174	16.58 - 24.49	3-5	46-62

Tanner scale of physical maturation [1-5] (1962).

General Data Collection and Procedures

Prior to each study, procedures were approved by the Ethics Committee. All subjects and their parents/guardians were thoroughly informed of the purpose, associated risks and details of the experimental procedures. Voluntary informed consent was obtained verbally and in writing from each subject and their family prior to testing (Appendix A). All subjects were also informed verbally and in writing of their right to withdraw from their research commitment at any stage of the research. This was in accordance to the Victoria University of Technology ethics committee on Human experimentation.

Laboratory Familiarisation

All subjects had a laboratory familiarisation session during which the specific testing equipment and protocols to be used throughout each study were introduced. During the familiarisation session subjects were given an opportunity to experience procedures such as riding the Monark™ cycle ergometer, running on the treadmill, spirometry measurements, using the respiratory valves, heart rate monitors, and having skinfold caliper measurements taken. A thorough description of the procedural details and demands of the study were presented and discussed to prospective subjects.

Respiratory Symptoms Survey

Prior to studies 2 and 3, all the asthmatic subjects were required to complete a Respiratory Symptoms Survey (Appendix A1). This helped to identify appropriate subjects for the study. The survey was attached to the written consent form described previously.

Anthropometric measurements

Anthropometric data (such as height and body mass) were measured to describe the physical characteristics of the subjects. The mean of three recorded trials was calculated and recorded as the measured value.

Body Mass: A Sauter E1200 electronic scale with a sensitivity of 0.001 kg was used for the measurement of body mass. Each subject was required to remove any heavy clothing and remain motionless while the digital display stabilised.

Height: A stadiometer calibrated in millimetres was affixed to the wall to measure height. Subjects stood flat on the floor (without any shoes and socks). The heels were required to be touching the wall. The head was erect and face directed straight ahead. During the height measurement the arms hang freely by the sides of the trunk with palms facing the thighs. A sliding wedge was placed on top of the head which formed a right angle with the stadiometer, the subject was requested to bend their knees and move away from under the block so height on the stadiometer could be easily read.

Skinfolds: Harpended skinfold calipers (scaled by 0.2mm) were used on all skinfolds. The value was read after 2 seconds which allowed the drift of the indicator needle to steady. All skinfolds were taken on the right side of the body, and the technique was standardised according to Harrison et al., (1988). The size of the skinfold included two thickness of the skin and subcutaneous fat but no muscle or fascia. Three measurements were taken at each site and the mean was recorded as the skinfold score.

Measurement sites:

1. Tricep skinfold (mm) - a vertical fold midway between the acromion process and olecranon process on the posterior side of the arm.
2. Suprailiac skinfold (mm) - an oblique fold on the iliac crest at the mid axillary line.
3. Abdominal skinfold (mm) - vertical fold adjacent to the umbilicus.
4. Subscapula skinfold (mm) - inferior angle of the scapula on the natural oblique fold.
5. Thigh skinfold (mm) - a vertical fold midway between the knee and hip joints with the person seated.
6. Biceps skinfolds (mm) - over the belly of the biceps with the arm hanging freely in extension.

Maturation Assessment

Maturational development was determined by a Tanner scale (1-5). Photos representative of stages in breast development in females and stages in genitalia development for males (Appendix B) were presented to the subjects where they were asked to make a self-rating assessment in private. Salivary testosterone was used in study three as an additional index of maturational status. Salivary testosterone is a non-invasive technique to evaluate androgenicity and is one of a number of indicators of sexual maturation which has been used successfully by researchers (Falgairette et al., 1991 and Walker et al., 1980).

Modes of exercise

Subjects in the first study used a Quinton™ (24-72) motorised treadmill. In the Second Study an Avionics ™ (E-10G) motorised treadmill was used by subjects. Prior to all tests, the treadmills were precisely calibrated by using the tachometer and revolution counter. A Monark ™ 814 cycle ergometer was used for the third study with the resistance controlled by an electronic force transducer (Extran 0-10kg) attached to the friction belt of the ergometer. The cadence of the pedal revolution rate and flywheel travel were measured via a light sensor with a 12-point photointerrupter disk fitted to the flywheel. An IBM computer was programmed to calculate the data from the exercise bouts. Output was computed at 50 hertz. The cycle ergometer was statically calibrated for zero and incremental weight resistances were calibrated using known weights.

Environmental Chamber

The third study was performed in a humidity and temperature chamber (Tabai TBL - 4RS - S Osaka, Japan). The temperature was held constant to ± 1.0°C at 12°C and the relative humidity was set at 35% with the constancy at ±3 % relative humidity. The absolute water content was less than 8 mg H_2O/L during all tests.

Determination of Lung Function

Each subject performed a test for Forced Vital Capacity (FVC) and Forced Expiratory Volume in One second (FEV_1) prior to all exercise tests. This was performed in a standing position and subjects were to begin with a maximal volume of exhaled air with a forced effort from a position of a full inspiration. The best result out of three trials was recorded. All post exercise spirometry tests involved only FEV_1 maneuvers. For the subjects to qualify for subsequent exercise testing each subject's pre- exercise flow rates were to be greater than 65% of the predicted value and within 10% of the usual pre testing value (Anderson, 1987). The procedures of the spirometry were in accordance with those advocated by the American Thoracic Society (statement on the standardization of spirometry, (1987).

The determination of lung function values were achieved by three different spirometry systems. (i) a Minato (Autospiro AS-500 Osaka Japan), (ii) a Vitalograph (compact spirometer #42.00), and (iii) a Welch Allyn (PneumoCheck Spirometer). Prior to all tests a three litre calibrated volume syringe was used for calibration purposes.

Provocation Tests

The Hyperosmolar Saline test was used in the first study to identify subjects with Exercise Induced Asthma. An electronic/ultrasonic Nebuliser (Compu - Neb™) was used which has a mist output of 5cc's/minute at nominal line voltage. The nebulizer canister was filled with 200 ml of hypertonic saline and refilled after nebulization to maintain a volume greater than 150 ml. The valve, the tubing (24 cm) and the canister were weighed prior to and following the challenge. While breathing at a resting respiratory rate subjects inhaled an ultrasonically nebulised aerosol of 4.5% saline via a two-way valve (Hans-Rudolph 1400). This occurred over increasing time periods (0.5, 1.0, 2.0, 4.0, 8.0, min). FEV_1 was measured for 60 seconds after each interval of exposure. If there was a discrepancy of more than 200 ml between the duplicate FEV_1 values, a third measurement was performed and subsequently the best of these two or three values was selected. The test was terminated when the FEV_1 fell by 20% or more from the value measured immediately before the challenge. The provoking dose to cause a 20% reduction in FEV_1 (PD_{20}) value represented the amount of aerosol in ml delivered (measured gravimetrically) to the inspired port of the valve. Classifications are outlined in table 3.2

Table 3.2. Classifications from the Hyperosmolar Saline test

PD_{20} was less than 2.0 ml	severe response
PD_{20} was between 2.1 - 6.0 ml	moderate response
PD_{20} was between 6.0 - 20.0 ml	mild response

(Adapted from Anderson et al, 1995).

The Exercise Challenge Test was performed in studies 2 and 3 to make assistance in the diagnosis of exercise induced asthma in the subjects. The typical exercise challenge test was modified so that a Peak $\dot{V}O_2$ could also be achieved. The exercise protocol in study 2 required the subjects to run on a motorised treadmill at a set grade of 15%. The treadmill speed was set at 4 kph for three minutes with subsequent speed increases in 0.5 kph every 3 minutes. After nine minutes of running at the speed of 5 kph subsequent increases in speed of 0.5 kph were imposed every minute until volitional fatigue. The aim of the testing was to achieve ventilation for six minutes above 60% of predicted Maximal Voluntary

Ventilation [MVV = predicted FEV_1 x 35 (Jones, 1982)] as this is the standard criteria for reaching the desired ventilation in an exercise challenge test. The tests were performed in a controlled environment with the relative humidity at 53% ±4% and the absolute water content of < 10mg H_20/L. In the third study the provocation test was performed on a Monark™ cycle ergometer within a temperature and humidity Environmental Chamber (Tabai™) with the water content below 10mg H_20/L. The protocol dictated that the subjects maintain a cadence of 80 rpm throughout the test. The initial workload was set at 50 watts for the first two minutes. Following this, the workload increased to the predicted workload to elicit 60% of MVV (Godfrey, 1974) which was maintained for a further three minutes. After reaching this stage the workload was increased by 25 watts every minute until volitional exhaustion. From a series of pre tests, it was decided that test termination should be denoted by an inability to maintain the 80 rpm cadence by 20 rpm for longer than 10 seconds.

Determination of metabolic data

In Studies One and Three the determination of metabolic data was performed by using an open circuit analysis of expired air (Consolazio, et al., 1963). The subjects, with nose clips in place, breathed through a Hans Rudolph valve which was connected to a mixing chamber via 5cm diameter lightweight tubing. Connected to the mixing chamber was a Pneumoscan ventilometer with a Mark 2 turbine flow transducer with an estimated accuracy of ±3%. The temperature of the gas was recorded by an electronic sensor in the mixing chamber connected directly to a computer. A sample of gas was pumped from the mixing chamber at 300 ml per minute and was analysed for the fractions of O_2 and CO_2 by Applied Electrochemistry analysers (S-3A (O_2) CD-3A (CO_2)). The carbon dioxide and oxygen analysers were calibrated by alpha gas samples (CIG, Melbourne) before and after each test. The metabolic equipment was connected via A-D converters to an IBM-PC which calculated the metabolic data at 15 second intervals.

In Study Two the determination of metabolic data was performed using an Jaeger Oxycon system. The oxycon is a system for the determination of cardiopulmonary capacity, ergospirometry and associated metabolic parameters. The system collected data using the open system approach and provided breath-by-breath measurements using an external volume sensor. The subject breathed via a digital volume transducer where the digital volume pulses were transmitted to the Oxycon. For analysis of the O_2 and CO_2 content a continuous gas sample was taken close to the mouth piece. The gas analysers and the simultaneously processing of the O_2, CO_2 and volume enabled breath-by-breath measurements and intra breath measurements. Similar to the aforementioned studies, in Study Two the carbon dioxide and oxygen analysers were calibrated by alpha gas samples (CIG, Melbourne) before and after each test. The data from the gas analysers and the volume transducer were pre-processed inside the Oxycon and transmitted via a 486PC.

Specific Warm-up Protocol

A specific warm-up protocol comprising of a stretching program for a 10 minute period was adopted prior to all testing. The static stretching regime that was implemented incorporated a slow stretch. This practice was adopted so that firing of the stretch reflex would be inhibited almost to the point of resistance. This stretch was encouraged to a range almost at where it was held for a 30 second period (Bloomfield et al., 1994). This action was repeated twice before the subject moved onto another region of the body. The specific regions that were stretched were hip and lower trunk, hamstrings, quadriceps, groins, hip flexors, calf, and achillies (Appendix C). This protocol was used for the asthmatics so that it would minimise the potential stimulus on ventilation which may have resulted if low intensity aerobic warm-up had been adopted.

Pre testing Protocol

The asthmatic subjects were requested to refrain from taking any medication before the tests by aerosol and orally for at least eight and 24 hours respectively. All subjects were also requested not to participate in any vigorous activity for 24 hours prior to each test and to withhold any food or fluid (exception for water) for two hours prior to exercise tests.

Medication Protocol

All subjects who were invited to participate in Study One had a history of successful treatment of sodium cromoglycate. Sodium cromoglycate was administered 30 minutes prior to all exercise tests via an electronic nebuliser (Ventalair™) with a flow rate of 6 - 8 litres per minute. In Studies Two and Three, medication was withheld prior to the exercise tests. Subjects who required medication after exercising were administered with a β_2 -agonist (salbuterol, 2 x 100μg) via a spacer (Volumatic™) (Glaxo Group Research, UK). Once the metered dose inhaler (MDI) was activated, the subject was immediately asked to fully inhale and hold his breath for 10 seconds before slowly exhaling. This procedure was repeated after one minute. The Volumatic™ was used to ensure visual proof that the metered dose inhaler had actuated correctly.

Blood Collection, Metabolic and Hormone Analytical Methods used in Study Three

To minimise the invasive nature of multiple blood sampling, in Study Three a catherization procedure was adopted by a practiced member of the research team. An indwelling catheter was inserted into a forearm vein while the subject was supine. A heparin lock was fixed to the hub of the cannula and occasionally

flushed with a minimal amount of hepranised saline. The blood drawn in each blood sample (7 ml), was ejected into a chilled glass tube and stored on ice. A further blood sample of 2.5 ml was collected in a syringe with a low dosage of heparin and immediately analysed for blood gases and acid-base measurements including PCO_2, PO_2, HCO_3, and pH. From each blood sample 1 ml was placed into lithium hepranised tubes and immediately separated. Following this, the plasma aliquot's were stored at -20^{o}C until analysed. A further 500 µl sample of plasma was combined with 3M PCA to be re-spun and the supernatant stored at -80^{o}C prior to analysis for lactate. Plasma lactate was determined in duplicate, using an enzymatic spectrophotometric technique (Lowry and Passinonneau, 1972). From the remaining 5 ml of venous blood 1 ml was collected in a lithium heparin tube containing a preservative for subsequent catecholamine analysis. The preservative was prepared by dissolving 2.25 g of ethyleneglycol - bis - (betaaminoethylether)N, N' - teraacetic acid (EGTA) and 1.5 g reduced glutathione (GSH) in 25 ml of normal saline (0.9% sodium chloride w/v) and adjusted to a pH range of 6-7.4 pH with 5-10M NaOH. Aliquots of this preservative (20µl per 1 ml of whole blood) were placed in tubes and stored on ice. The appropriate volume of blood was added to the tubes , mixed gently, and spun in a centrifuge at 4^{o}C for 15 minutes at 1500 rpm (900g). The supernatant was transferred to tubes and refrigerated (-80^{o}C). Adrenaline and noradrenaline concentrations were analysed by a modification of the single isotope [^{3} H] radioenzymatic assay of Passon and Peuler, (1973) as described in Amersham™ Catecholamine research assay system (Kit TRK 995). Subsequently each sample was counted for 10 minutes on a beta counter (Packard Tri-Carb 400™). Blood gas and acid-base measurements were determined from a blood gas analyser (ABL 30, Radiometer, Copenhagen). Sampling occurred at pre-determined intervals following each exercise bout.

Testosterone concentration in saliva was selected as an index of sexual maturation. The subject was required to provide 2 ml of saliva in a 5 ml container for three consecutive mornings which was then stored at -20^{o}C. Salivary testosterone was analysed by a radio-immunology method using a commercially available kit DPC Coat-A-Count Total Testosterone (TKTT1).

Peak oxygen uptake protocol

In Study One, the peak oxygen uptake protocol was measured using an incremental exercise protocol on a motorised treadmill. The grade remained constant at 6% throughout the test. The running speed commenced at 5 kph and an increment of 1 kph every minute was added until volitional exhaustion. In Study Two, a motorised treadmill was also used however, a different protocol was adopted. The protocol which was adopted, allowed for the determination of steady state responses to the individual heart rate and running speed/workload relationships. Subsequent linear regression analysis of this data enabled the prediction of workload that would elicit heart rates of approximately 175 bts. min^{-1}. In this protocol the

treadmill's grade remained constant at 15%. The initial speed was set at 4 kph for three minutes. The speed was then increased to 4.5 kph for three minutes followed by 5 kph for three minutes. After this point the speed was increased 1 kph every minute until test termination or volitional exhaustion. The Third Study was performed on cycle ergometer (Monark™ 814). The testing protocol consisted of 25 watt increments every minute until the subject achieved 60% of the predicted MVV for a period of three minutes. After this, the subject continued cycling with increments of 25 watts every minute until volitional exhaustion.

The criteria for reaching maximal effort included a plateau of oxygen uptake (less than $2ml.kg^{-1}$ min^{-1} increase with work) (Taylor et al., 1955). The criteria of achieving a plateau in oxygen uptake with increasing workload was applied with caution in that the majority of child-based populations may not display an oxygen uptake plateau index of capacity (Rowland, 1992). When a plateau of O_2 uptake was not evident, additional criteria were used. These included a heart rate value greater than 95% of predicted maximal heart rate, and a respiratory exchange ratio (RER) greater than 1.05 (Zwiren, 1989). Subjects were verbally encouraged so that maximal effort was expected from all maximal effort tests. A member of the research team was positioned close to each subject while running on the treadmill to ensure complete safety throughout the exercise tests.

Steady State Submaximal Testing

During Study One the subjects performed a series of 5-6 six minute of submaximal steady state running at randomised speeds predicted to induce a steady state during each run. The subjects performed two submaximal steady state tests per day with a minimum of 30 minutes rest between tests. The $\dot{V}O_2$ data

from the final two minutes of the submaximal tests was used to help obtain the steady state value. More specifically steady state oxygen uptake was obtained from a non-linear exponential equation (KaleidaGraph, 1989). Steady state tests where $\dot{V}O_2$ ($ml.kg^{-1}min^{-1}$) varied by more than 2 $ml.kg^{-1}min^{-1}$ in the final two minutes were rejected. Individual least squares linear regression equations were constructed from the submaximal running speeds and their associated steady state oxygen uptakes. The linear relationship between treadmill speed and oxygen uptake enabled a linear equation to be constructed to predict oxygen demand of supramaximal workloads. In Study Two, three submaximal workloads were designed in the early stages of the $\dot{V}O_2max$ test. The steady state heart rates for these three submaximal workloads, were the meaned values for the last three 30 second intervals of each workload. These steady state heart rates and their associated workloads enabled the computation of a standard, least squares linear

regression equation to predict the workload that would elicit a heart rate of 175 beats per minute. The prescribed workload was subsequently used as the baseline value in the continuous and for calculations of high intensity workloads in the intermittent tests.

Supramaximal runs

The prediction of speeds which represented energy requirement of 110 and 130% of $\dot{V}O_2$ peak used data from both peak oxygen uptake tests and submaximal $\dot{V}O_2$ responses. The supramaximal speed was obtained with an inversion of the equation $y = a + b(x)$, to $x = (y-a)/b$; where $y = \dot{V}O_2$, and x = speed (Appendix D). The peak oxygen uptake scores were used to determine estimates of 110 and 130% for each subject's equation. Prior to and during both supramaximal intensity tests subjects were encouraged to run to exhaustion. Douglas Bags were used to collect expired air for the duration of these tests. Prior to the commencement of the supramaximal run the treadmill was moving at the calibrated set speed and the subject held onto the handrails with his legs straddling the moving belt. A member of the research team was "spotting" the subject from behind with his legs straddling the treadmill belt. The subject was given a command to go. At this moment the subject was to adjust to the set speed with assistance from holding onto the handrails for only a second before commence free running. The test would terminate when the subject reached for the handrail. All subjects were provided practice at running at various high speeds on the treadmill several days prior to the testing and 30 minutes before the run on the actual testing day. The two supramaximal runs were performed on separate days.

Analysis of expired air during supramaximal exercise testing

In Study One expired gases from supramaximal tests were measured using a Douglas Bag collection technique. The expired air is collected via a one-way valve into the Douglas Bag which was connected to a three-way stopcock and stopwatch. The stopwatch automatically started and stopped when the stopcock was turned. Subsequently the fractions of O_2 and CO_2 were analysed on the Applied Electrochemistry Analyser (Amatek™) at a sampling rate of 300 $ml.s^{-1}$ for both O_2 and CO_2. A Parkinson-Cowan™ ventilometer was used to measure the volume of expired air. The ventilometer was calibrated against a Tissot spirometer. The calculations from the raw data were entered into a specifically designed program on a PC for the Haldene Transformation and provided measurements of $\dot{V}O_2$ ($l.min^{-1}$ and $ml.kg^{-1}$ min^{-1}), $\dot{V}CO_2$ ($l.min^{-1}$), $\dot{V}E$ ($lmin^{-1}$) and RER from the supramaximal running efforts.

Rating of Perceived Exertion

In Study Two, the Borg scale was used to assess the subjects level of perceived stress immediately upon the completion of each continuous or intermittent exercise bout (Table 3.2).

Table 3.2 Borg Scale for Rating of Perceived Exertion

0	Nothing at all
0.5	Very, very weak
1	Very weak
2	Weak
3	Moderate
4	Somewhat strong
5	Strong
6	
7	Very strong
8	
9	
10	Very, very strong (maximal)

(Adapted from Borg, 1982)

Summary of Protocol

Table 3.3 A summary of the protocols used in the three studies.

Study	Summary of Protocol
One	• Asthmatic subjects diagnosed with asthma via Hypersaline Challenge test. • $\dot{V}O_2$ peak test performed on a treadmill (Open Circuit Spirometry using Online PC) • Six submaximal steady state tests • Supramaximal tests at 110, and 130 % $\dot{V}O_2$ peak. • Spirometry tests pre and post exercise.
Two	• $\dot{V}O_2$ peak test/Exercise challenge test performed on a treadmill to identify subjects with EIA. • Steady state values were obtained from this test to be used in the prediction of a workload that would elicit a heart rate of 175 bpm. • Spirometry tests pre & post exercise. • Four exercise protocols were randomly assigned. 1) 6 min Continuous treadmill running at 15% grade to elicit a heart rate of 175 bpm. 2) 6 min Intermittent running test double the speed of the 6 min cont. 30 s run - 30 sec. rest. 3) 6 min Intermittent running test double the speed of the 6 min cont. 10 s run - 10 sec. rest. 4) 6 min Intermittent running test triple the speed of the 6 min cont. 10 s run - 20 sec. rest.
Three	• $\dot{V}O_2$ peak test/Exercise challenge test performed on a Monark™ cycle ergometer to identify subjects with EIA. • The three high intensity protocols were randomly assigned. 1) 1 x 30 s Wingate Anaerobic Test on a Monark™ cycle ergometer. 2) 2 x 15 s modified Wingate Anaerobic Test on a Monark™ cycle ergometer. 3) 3 x 10 s modified Wingate Anaerobic Test on a Monark™ cycle ergometer. • Pre and Post spirometry measurements. • Pre and Post analysis of blood borne indices of exercise metabolism

Overview of Statistical Presentation of the Data

Data were entered in a format which was suitable for analysis by either SPSS or Microsoft EXCEL packages installed on an IBM-PC. All data are presented in means and standard errors of the mean (M ± SEM) and the performance data were analysed by an univariate approach with repeated measures design. In all studies, the two levels of condition; the asthmatic and non-asthmatic were examined for differences

in the mean responses elicited under varying anaerobic exercise challenges. (e.g. the two supramaximal speeds in Study One). Respiratory and blood borne responses were repeated over time in recovery measurements. Newman-Keuls post hoc analysis tests were conducted when required. The .05 level of significance was applied for all general statistical analysis.

Table 3.4 Summary of the statistical design

Study	Outline of ANOVA	Description of ANOVA
One	one-way	Physical characteristics
	2 x 2	Condition by supramaximal intensity by time
	2 x 2 x 3	Condition by FEV_1 responses by time
Two	one-way	Physical characteristics
	2 x 4	Condition by intensity
Three	one-way	Physical characteristics
	2 x 3	Condition by intensity
	2 x 3 x 1	Condition by FEV_1 responses by time
	2 x 3 x 3	Condition by blood responses by time

Chapter Four

Study One

Anaerobic Characteristics and Performance of Pre-Pubertal Asthmatic and Non-Asthmatic Males

Anaerobic Characteristics and Performance of Pre-Pubertal Asthmatic and Non-Asthmatic Males

ABSTRACT

This study examined the anaerobic responses of pre-adolescent asthmatic males and compared these characteristics with non-asthmatic males of a similar pubertal status. Anaerobic characteristics were measured using the accumulated oxygen deficit (AOD) of 10 asthmatics (mean age 10.9 years) and 10 non-asthmatics (mean age 11.1 years). Prior to participating in the study, the asthmatic subjects all tested positively to a hypersaline provocation test. Before all subsequent exercise tests the asthmatic children were administered 20mg of sodium cromoglycate via a nebuliser. Forced Expired Volume in 1 second (FEV_1) was measured before and after exercise and the post exercise value was expressed as a percentage of the pre exercise value. In order to determine the anaerobic characteristics, subjects were required to run to exhaustion at speeds predicted to represent energy requirements equivalent of 110% and 130% of their $\dot{V}O_2$ peak. The asthmatic children's mean AOD values for 110% and 130% when expressed relative to body mass ($ml.kg^{-1}$) were 53.23 $\pm$ 4.02 and 50.60 $\pm$ 2.81 $ml.kg^{-1}$ respectively, and the comparable values for the non-asthmatics were 51.59 $\pm$ 2.66 and 47.04 $\pm$ 3.44 $ml.kg^{-1}$. There were no statistically significant differences in anaerobic characteristics measured by AOD values ($P > 0.05$) between intensities and groups. FEV_1 data revealed that up to 15 minutes post exercise, there was no bronchoconstriction occurring in either group under either of the test intensity conditions.

Introduction

Exercise-induced asthma (EIA) can be a limiting factor for enjoyment of, and subsequent participation in physical activity by children. Depending on the response to the diagnosis of EIA, children and/or their parents can potentially adopt modifications to their activity patterns which may result in deconditioning. In terms of examining the aerobic exercise performance capacity of children the research is equivocal with data showing that active asthmatic children have similar aerobic power compared with healthy active children (Fink et al., 1993) and non active asthmatics have reduced aerobic power when compared with their healthy active counterparts (Varray et al., 1989). Similarly, there has been limited research comparing the anaerobic characteristics of the asthmatic and the non-asthmatic child. Previous work examining the maximal anaerobic power of asthmatic children using the Wingate anaerobic test has indicated a lower anaerobic power when compared to their non-asthmatic counterparts (Karila et al., 1992). The Wingate anaerobic test by design examines peak and mean power performances over a fixed short term period of thirty seconds. High intensity performances beyond this time frame have not been investigated in asthmatic populations. The body of knowledge on the anaerobic responses to high intensity exercise in young populations with EIA is limited. Therefore, the purpose of the study was to investigate active children with EIA and their anaerobic performances to exhaustion compared with a matched normal group of non-asthmatic children. The method used to measure the anaerobic characteristics was the accumulated oxygen deficit (AOD). The measurement of the AOD as a measure of anaerobic characteristics, has not previously been investigated in the asthmatic child. Under "supramaximal exercise conditions" the measurement of AOD has been advocated to provide a estimation of energy release from anaerobic sources (Bangsbo et al., 1990, Medbø et al., 1988).

Purpose

To compare anaerobic capacities of asthmatic and non-asthmatic pre-adolescents males using the accumulated oxygen deficit method.

Method

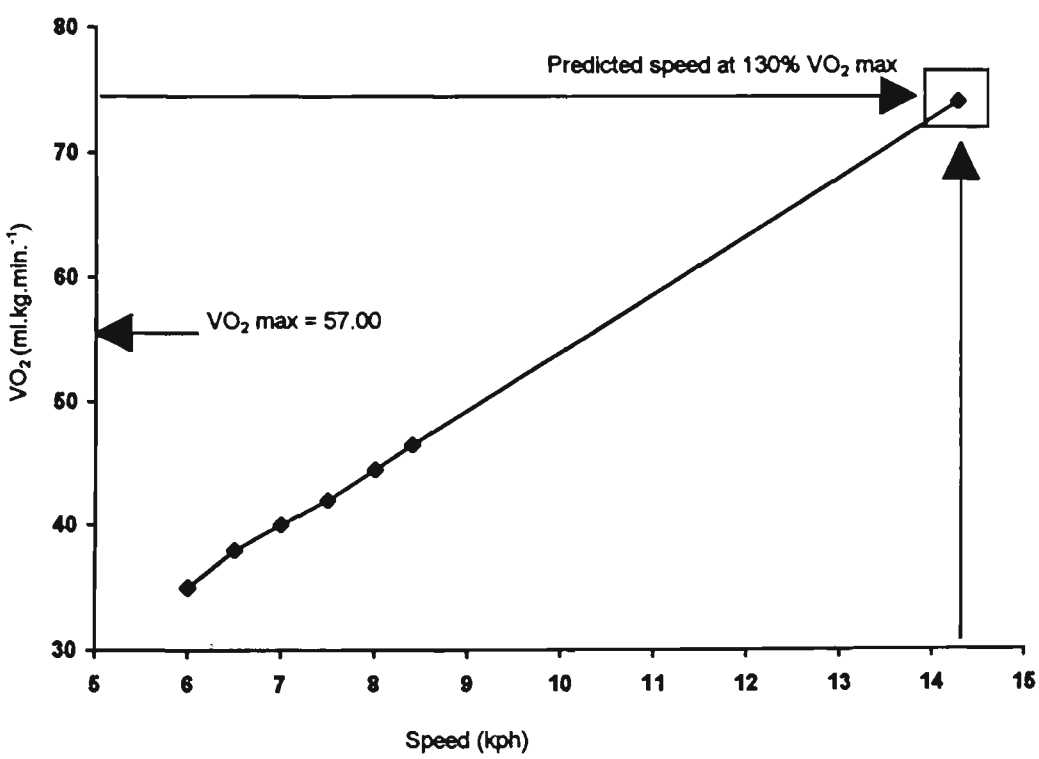
Ten asthmatic males (mean age 10.9 $\pm$ 0.2 years) and ten non-asthmatic males (mean age 11.1 $\pm$ 0.2 years) from local primary schools volunteered to participate in this study. All subjects were physically active and took part in 2-3 organised sessions of activity per week. Informed consent was obtained from the subjects and parents/guardians which was in accordance with the guidelines established by the Ethics Committee from the University (Appendix A).

The Hyperosmolar Saline (4.5% NaCl) Provocation Test was used to assist with the classification of the asthmatics (Anderson, 1987). The subject inhaled an ultrasonically nebulised aerosol of 4.5% saline through a two-way valve for increasing periods (0.5, 1.0, 2.0, 4.0, 8.0 minutes). The forced expired volume in one second (FEV_1) was measured 60 seconds after each interval of exposure. The test was terminated when the FEV_1 fell by 20% or greater than the value measured immediately before the challenge provocation test. A dose-response curve was constructed and the doses which provoked a 10, 15 and 20% fall in FEV_1 were reported as PD_{10}, PD_{15} and PD_{20}, respectively (PD = provoking dose). The PD value represents the amount of aerosol in millilitres delivered (measured gravimetrically) to the inspired port of the valve. A fall of 15% or greater was regarded as abnormal as it was greater than two standard deviations beyond the mean value for percentage fall in the FEV_1 observed in normal subjects (Anderson, 1987). Following the provocation tests all subjects who tested positively were invited to participate in the study. The criteria for the subjects' inclusion in the study were: (i) testing positive to the provocation test, (ii) being physically active (i.e. regular participation in school Physical Education classes and at least two other weekly sessions of organised sport participation.) and (iii) being a male between 10 to 11 years of age.

Prior to testing a familiarisation session was given for subjects. Throughout the study the treadmill, remained at a constant 6% inclination. The asthmatic subjects were administered with 20mg of sodium cromoglycate by a nebuliser (Ventalair ™, Allersearch) 30 minutes prior to all exercise tests. On the first visit to the laboratory each subject performed a peak oxygen uptake test on the treadmill with a protocol starting at 6 km/h, with subsequent one km/h increments each minute until volitional exhaustion. During the next three to four visits, the subjects performed a series of 6-8 minutes of steady state running at randomised submaximal speeds. The subjects performed two submaximal steady state tests per day with a minimum of 30 minutes of rest between the exercise bouts. Individual linear regression equations were constructed from the submaximal running speeds and their

associated steady state oxygen uptakes (Carlson and Naughton, 1993). A detailed example of this technique has been described previously by Medbø et al. (1988) and Chapter Three (Appendix C). The same principles outlined by Medbø et al. (1988) and Carlson and Naughton (1993) have been applied to a running protocol on a motorised treadmill. As cycling produces very local muscular fatigue, the treadmill was chosen for the work task as it was felt that running would be more acceptable to the subjects who would then readily exercise to fatigue. The prediction of speeds representing 110 and 130% of maximal effort was performed from linear regression equations constructed from data of both the peak oxygen uptake test and the individual submaximal VO_2 /running speed responses (Figure 4.0). The supramaximal speed was obtained with an inversion of the equation $y = a + b(x)$, to $x = (y-a)/b$; where $y = VO_2$, and x = speed. The peak oxygen uptake value was used to determine the running speeds estimated to be at 110 and 130% for each individual subject. On two separate occasions supramaximal tests were conducted. These tests required the children to run to exhaustion at 110 and 130% of maximal effort.

Figure 4.0 Prediction of supramaximal treadmill running speeds from submaximal steady state VO_2.



Prior to the supramaximal runs each subject performed a forced expiration from a full inspiration into a spirometer (Minato Autospiro AS- 500) to measure the FEV_1. Prior to each supramaximal test, subjects were required to be within 10 % of their previous best FEV_1 baseline value before commencing the exercise test. Each subject performed the spirometry test twice and the highest value was recorded. Approximately 30s separated these tests. Post exercise spirometry tests were conducted at 5, 10, and 15 minutes. The open-circuit metabolism technique was used to obtain metabolic measurements for submaximal and peak oxygen uptake tests (Carlson and Naughton, 1993). During the supramaximal tests expired air gases were collected in Douglas Bags which were subsequently analysed for the fraction of CO_2 and O_2 using Applied Electrochemistry (Amatek) analysers. The test was terminated when subjects could not maintain the running cadence and used the hand rails of the treadmill for support. Throughout the supramaximal test the subjects were encouraged verbally to run to exhaustion.

A series of two-way ANOVAs was conducted to determine if significant differences existed across the two intensities (AOD tests performed at 110% and 130% of maximal effort) and between the two groups (asthmatics and non-asthmatics) (SPSS). A further series of two-way ANOVAs was conducted on the respiratory measures with post exercise time as the repeated measure. The 0.05 level of significance was adopted for all testing.

Results

Table 4.0 contains the data which profiles the descriptive and maximal effort testing characteristics of the two groups. There were no significant differences between the asthmatic and non-asthmatic children in age, mass and height ($P>0.05$) (Appendix E1.1). Results from the peak $\dot{V}O_2$ tests are also presented in Table 4.0. The self selection of asthmatic and non-asthmatic subjects for a study of this nature is perhaps reflected in the relatively high maximal aerobic power score. The data were indicative of subjects achieving their maximal aerobic effort according to the criteria advocated by Zwiren, (1989). No differences were found between asthmatic and non-asthmatic children in both relative and absolute peak $\dot{V}O_2$ ($ml.kg^{-1}.min^{-1}$ and $l.min^{-1}$) and respiratory exchange ratio (RER). All the subjects attained maximal heart rates which exceeded 95% of age- predicted maximum and achieved an RER in excess of 1.05 at peak $\dot{V}O_2$.

Table 4.0 Descriptive and maximal effort testing characteristics

VARIABLE	SUBJECTS ASTHMATICS		NON-ASTHMATICS	
Age (yrs)	10.9	(0.2)	11.1	(0.2)
Mass (kg)	38.19	(2.30)	34.57	(2.21)
Height (cm)	141.9	(2.7)	141.1	(1.84)
Peak VO_2 ($l.min^{-1}$)	2.11	(0.07)	2.12	(0.07)
Peak VO_2 ($ml.kg^{-1}.min^{1}$)	55.51	(1.90)	60.98	(2.18)
RER	1.11	(0.02)	1.15	(0.07)
Heart rate (bpm)	204*	(1)	210	(2)

(M±SEM) *significant difference, $P < 0.05$

RER: Respiratory Exchange Ratio

A= asthmatics NA= non-asthmatics

The results of the anaerobic performance and characteristics testing are presented in Table 4.1 and (Appendix E1). The anaerobic characteristics measured by the AOD expressed in absolute terms (litres) and relative to body mass ($ml.kg^{-1}$) revealed no significant differences between the two groups of males nor any significant differences between the two supramaximal testing conditions. The interpretation of results may be limited by the low effect size for both tests at 110 and 130% AOD, (*d* .31 and .32, respectively). The running speed required to elicit an energy requirement of 130% $\dot{V}O_2$ was significantly greater than the speed calculated to represent 110% of maximal effort. Within the groups the running speeds were significantly faster in the non asthmatic boys at both 110 and 130% $\dot{V}O_2$. The mean running speeds for both groups at 110 and 130% $\dot{V}O_2$ were 11.3 km/h and 13.5 km/h, respectively. No significant differences were observed in the peak heart rates elicited by the two groups at either of the testing conditions. Running time to exhaustion was significantly higher in both groups at the 110% $\dot{V}O_2$ when compared to the 130% $\dot{V}O_2$ max condition. The mean time to exhaustion was not significantly different between the groups at each of the two supramaximal running conditions. The mean times for running to exhaustion in both groups for the 110% and 130% $\dot{V}O_2$ testing conditions were 66.75 and 88.55 seconds, respectively. Results for the peak RER measurements demonstrated no difference between the two groups, nor between the two testing exercise intensities.

Table 4.1 Anaerobic characteristics following supramaximal runs to exhaustion in asthmatic and non-asthmatic children

VARIABLE	CONDITION			
	110% $\dot{V}O_2$		130% $\dot{V}O_2$	
	A	NA	A	NA
AOD	2.08	1.77	1.96	1.6
(Σ L)	(±0.25)	(±0.12)	(±0.21)	(±0.13)
AOD	53.23	51.59	50.60	47.04
($ml.kg^{-1.}$)	(±4.02)	(±2.66)	(±2.81)	(±3.44)
Run speed	10.8 #	11.7 *	12.75 #	14.2
(km/h)	(±0.48)	(±0.41)	(±0.64)	(±0.49)
Run time to	173.1 #	160.4	88.4	78.7
exhaustion (sec)	(±16.31)	(±15.27)	(±5.91)	(±7.11)
Peak Heart Rate	195.6	199.6	192.3	197.3
(bpm)	(±1.83)	(±2.32)	(±2.12)	(±2.04)
RER	1.09	1.05	1.06	1.04
	(±0.02)	(±0.02)	(±0.02)	(±0.02)

A= asthmatics NA= non-asthmatics

M(± SEM)

significantly different, $P < 0.05$ RER: Respiratory Exchange Ratio

# denotes difference between asthmatic and non-asthmatic males, $P < 0.05$

* denotes differences between the intensities of the supramaximal runs, $P < 0.05$

Figure 4.1 presents the 5, 10, and 15 minute post exercise respiratory responses of FEV_1. These FEV_1 values are expressed as a percentage of the testing measurements determined immediately prior to the supramaximal runs. It can be seen that following the two high intensity exercise bouts the repeated measures of FEV_1 demonstrated no significant decline in respiratory function in either the asthmatic or non asthmatic children. In addition there was no effect of test intensity response in the FEV_1 responses of the two groups.

Figure 4.1 Forced expired volume in 1 second (FEV_1) responses of children pre and post supramaximal exercise.

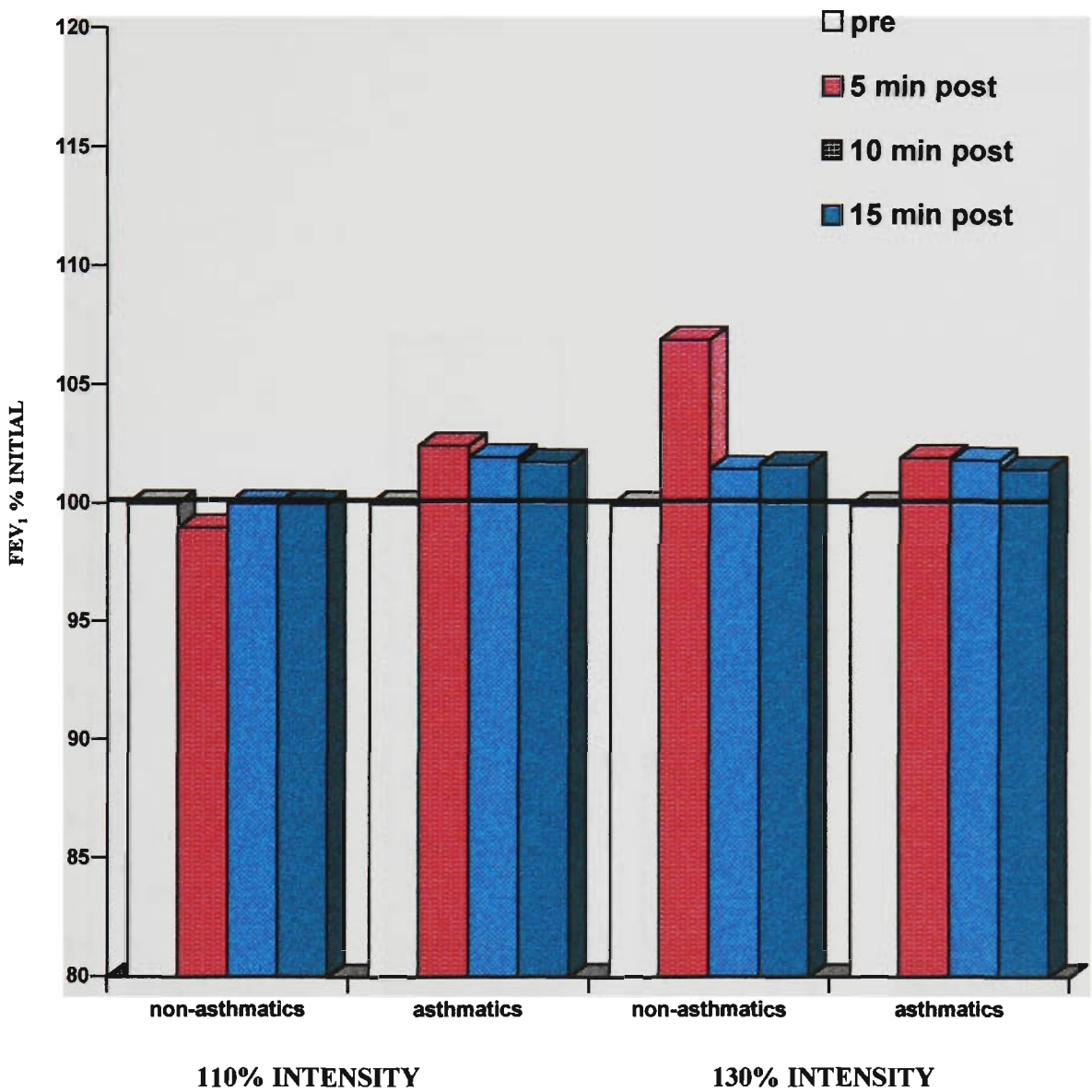
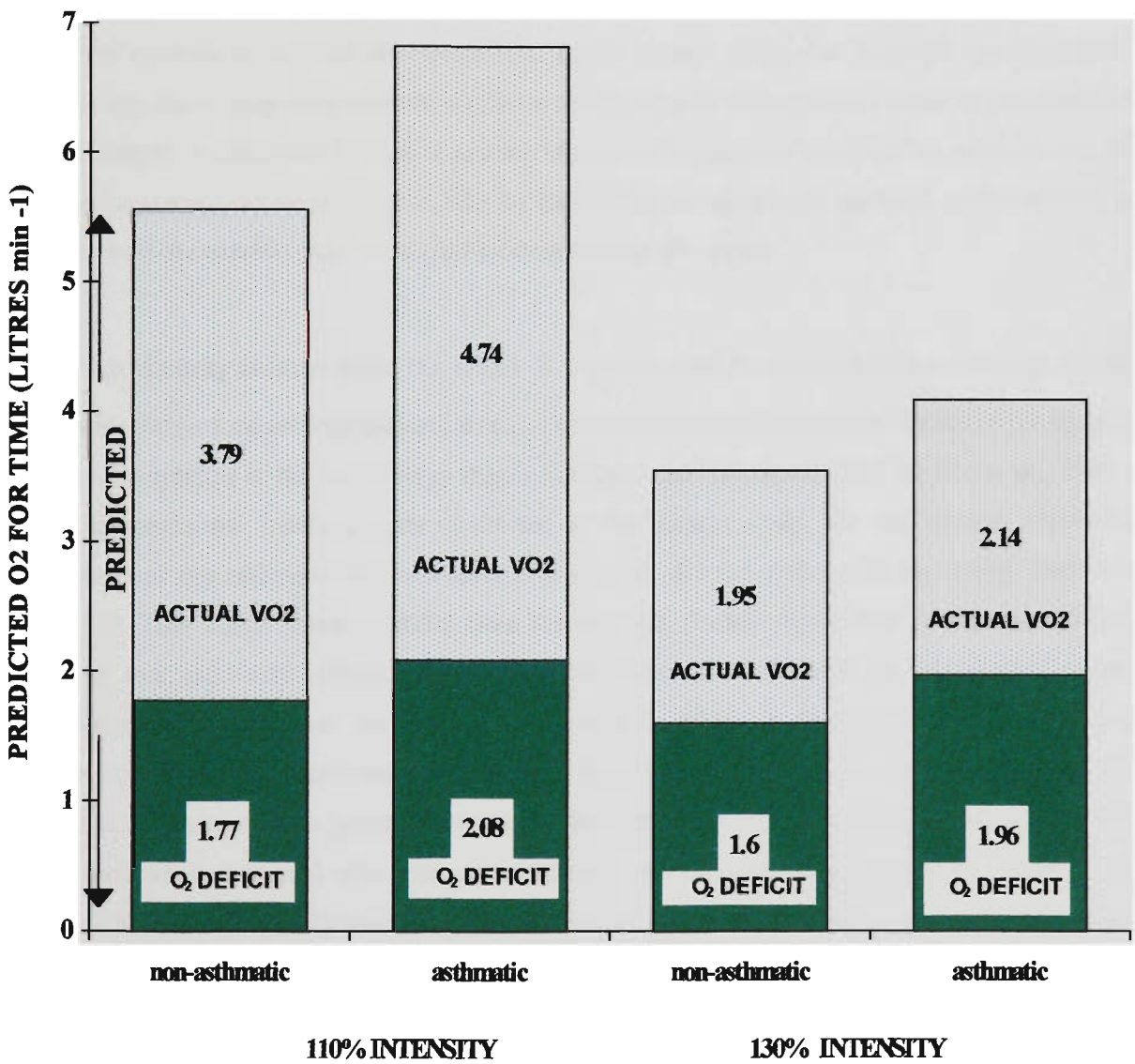


Figure 4.2 Actual VO_2 ($l.min^{-1}$) and O_2 deficit (litres) values within predicted energy costs at 110% and 130% of maximal effort predicted.



Discussion

This study used the AOD method to compare the anaerobic responses of young asthmatic and non-asthmatic males. It was demonstrated that no differences existed in the measured anaerobic characteristics of the two groups. The AOD values which were determined from two supramaximal testing protocols also revealed that different intensities did not produce significantly different measurements of AOD. The non significant difference between the AOD results from the two supramaximal intensity tests may support the observation of a plateau denoting the presence of an "anaerobic capacity" (Medbø et al., 1988).

The differences in peak $\dot{V}O_2$ and AOD values of the boys in the present study when compared with those reported for a similar age group of boys by Carlson and Naughton (1993) may be explained in the mode of exercise selected by the researchers. In the present study, the treadmill running rather than cycle ergometry may have allowed a greater recruitment of active muscle mass to contribute to metabolic output. A limitation in studies seeking volunteers in children is always the self selection of the young people willing to participate, who by their nature tend to enjoy physical activity and as a result may be more conditioned than a total random sample of children.

During high intensity exercise when the actual $\dot{V}O_2$ consumed is expressed as a percentage of that predicted for the performance an indication can be obtained of the relative contributions of the aerobic and anaerobic systems to the total energy supply (Carlson and Naughton, 1993, Medbø et al., 1988). In both supramaximal treadmill tests conducted in the present study, the aerobic and anaerobic contributions of the asthmatic and non-asthmatic subjects did not differ with the energy demands (Figure 4.2). This would appear to differ from the previous finding reported by Varray et al. 1989, who found that asthmatic children have an aerobic limitation influenced by bronchoconstriction within the airways throughout the final phase of exercise which is compensated by a significant anaerobic contribution. In agreement with Varray et al. (1989), Karila et al. (1992) demonstrated that the asthmatic children had a lower general anaerobic fitness (peak power obtained using the force velocity test) when compared with their non-asthmatic counterparts. The research of Varray et al. (1989) and Karila et al. (1992) was conducted without pre-medication of sodium cromoglycate or a β-agonist being administered to the asthmatic subjects. As the present study was focusing on "functional" performance, it was decided to follow "normal" pre-medication procedures. More specifically, the AOD method which involved running on a treadmill was identified as being more applicable to active children, than performing a high velocity power test on a stationary cycle ergometer. The natural play activity of children and demands of common team sports involve intermittent efforts of high intensity. These efforts may be supramaximal in terms of the individual's maximum aerobic power ($\dot{V}O_2$ max). The intention of the present study was to determine whether being asthmatic has influenced or compromised the anaerobic characteristics of the young male

subjects. The study demonstrated no difference in anaerobic performance with asthmatic and non asthmatic children. It is possible however, that if the asthmatic children performed the supramaximal exercise without any pre-medication then a different result may have occurred. In agreement with the work of Varray et al. (1989), the pilot work which preceded this study demonstrated that the aerobic system may be compromised in some asthmatics who experienced difficulty in achieving steady state without pre-medication. The AOD method strongly relies on the submaximal steady state oxygen uptake data to determine the linear regression of running speed and energy demand. Through the administration of sodium cromoglycate prior to supramaximal exercise tests the possibility of hypoxemia occurring for the asthmatics was reduced. It is postulated that during the supramaximal running tests the oxygen deficit results may have remained the same with, or without the administration of sodium cromoglycate because the AOD would not have been impaired if broncoconstriction occurred throughout the exercise bout. This postulation is supported by previous investigations of AOD testing conducted under hypoxic conditions resulting in no change in the AOD values to those determined under normoxia (Medbø et al., 1988). Research of this nature however, is yet to be reported in young asthmatic populations. AOD performances represent the estimates of ATP release and resynthesis under high intensity exercise demands. It is hypothesised that the rate of energy release without the muscle is largely reflective of the state of training of the active muscle rather than the effects of respiratory based complications of EIA. Differences between groups would therefore be expected to be negligible. Medbø and Burgers (1990) demonstrated significant differences in AOD values following training in male and female adults. Sensitivity to training anaerobically reported high AOD values, however it remains unknown in children and adolescence.

In conclusion, because the results indicated no differences between the performances of the two groups, it can be postulated that this group of asthmatic and non-asthmatic children may have had an equal ability to exercise at high intensity when a preventative medication is administered to the asthmatic child. No evidence of respiratory distress was observed in any of the subjects following the exercise tests and there was no differences in the FEV_1 values between the groups following the runs to exhaustion. Therefore, both performance and respiratory data combine to demonstrate similar anaerobic responses to high intensity exercise in the asthmatic and non-asthmatic males recruited in the present study. Anaerobic challenges in the asthmatic child may therefore be an appropriate form of exercise prescription when adequate preventative medicines are administered.

Chapter Five

Study Two

Examining the Influence of Repetitive, High Intensity Work (for 6 minutes duration) on Children with Exercise Induced Asthma

Examining the Influence of Repetitive, High Intensity Work (for 6 minutes duration) on Children with Exercise Induced Asthma

Abstract

This study examined the influence of various repetitive, high intensity treadmill running protocols on children with exercise-induced asthma (EIA). Ten active asthmatic children (five male and five females) with a mean age of 11.1 years were compared with eight active non-asthmatic children (five male and three females) with a mean age of 10.9 years. The asthmatic subjects were diagnosed as having EIA from a peak $\dot{V}O_2$ test. Whenever the forced expiratory volume in one second (FEV_1) values demonstrated a 15% or greater reduction from pre-exercise FEV_1 values the subjects were classified as having EIA. Subjects performed four treadmill running exercise tests on separate days within a two week period and were requested to withhold any bronchodilator medication eight hours prior to testing. The four test protocols were designed to produce equal amounts of work and elicit a ventilatory stimulus greater than 60% of predicted maximal voluntary ventilation (MVV). The four protocols required a total of six minutes of exercise and incorporated different speeds and durations. The test protocols comprised of:

1 a six minute continuous run

2 the speed from test one was doubled and subjects ran repeatedly for 30s and rested for 30s until six minutes duration was completed.

3 the speed from test one was doubled and the subjects ran for 10 s and rested for 10s until a six minute duration was completed.

4 the speed from test one was tripled and the subjects ran for 10s and rested for 20s again until a six minute duration was completed.

Analysis of data from all four protocols indicated that there were no significant differences between respective values for asthmatics and non-asthmatics for HR (175 and 182 bpm), VE (39.6 - 46.0 $L.min^{-1}$), or $\dot{V}O_2$ (37.3 - 40.9 $ml.kg^{-1}\ min^{-1}$) ($P > 0.05$ ANOVA). The percent fall index in FEV_1 over the four tests ranged between 20 and 34% for the asthmatics and between -0.375 and -0.625% for the non-asthmatics. Subsequently there was a significant difference between asthmatics and non-asthmatics in the % fall index in FEV_1. Post-hoc analysis indicated that this difference had occurred between the 30 x 30 intermittent protocol and 10 x 10 intermittent protocol for the asthmatic subjects ($P < 0.05$ ANOVA). One of the major findings from this study was the indication that the intermittent exercise may be as potent as continuous exercise in the provocation of EIA if the metabolic and ventilatory stresses are matched.

Introduction

Findings that continuous exercise being much more asthmogenic than intermittent exercise are common within the literature (Edmunds et al., 1978, Eggleston and Guerrant, 1976, Godfrey 1975, Jones et al., 1963, McKenzie et al., 1994, Morton et al., 1982, Wilson & Evans 1981). Silverman and Anderson (1972), demonstrated that maximal EIA responses in asthmatic subjects could be produced from continuous running 6 to 8 minutes and maintaining an intensity of 60-85% $\dot{V}O_2max$ with the heart rates reaching 170 to 175 bpm. Exercise bouts shorter than two minutes duration appear to fail to cause large airway obstruction (Jones et al. 1962). This has been further supported by the observation that bronchodilation can result from intermittent exercise (de Bisschop et al., 1992, Godfrey 1975, Schnall & Landau 1980, Silverman et al., 1972). Previous findings from Schnall and Landau, (1980), found that six asthmatic subjects aged between 12 and 31 years who performed repeated bouts of 30-second sprints with recovery periods of 150 seconds produced no evidence of bronchoconstriction. The workload duration in the study of Schnall and Landau (1980) however, was not reflective of the natural play activity patterns of children and nor was it effective of the intermittent efforts common to Australian team sports popular among children (Naughton and Carlson, 1990). These sports involved efforts of high intensity and could be described as supramaximal in terms of the individual efforts required. A study conducted by Morton et al. (1982) examined the responses of 27 asthmatic subjects (aged from 12 -35 years) who performed a continuous treadmill run for six minutes (85 % of their predicted maximal heart rate) as well as four different intermittent exercise protocols. The results showed that the greatest decrement in pulmonary function was observed following the continuous exercise. Morton et al. (1982) found when exercise was performed intermittently, (running 36 bouts of 10 seconds work with 30 seconds rest at the same workload as the continuous) caused less airway constriction when compared to the other intermittent protocols involving less repetitions. The four protocols they utilized were:

1. 3 mins. running, 5 mins. rest, 3 mins. running (same as the continuous workload)
2. 20 repetitions of 10s running, 30s rest (175% of workload used in the continuous test)
3. 10 repetitions of 20s running, 60s rest (175% of workload used in the continuous test)
4. 36 repetitions of 10s running, 30s rest (same as the continuous workload)

The design of the exercise protocols used by Morton et al (1982) were more likely to represent typical sporting exercise bouts compared with those used by Schnall and Landau (1980). In the study conducted by Schnall and Landau (1980) there were however no measurements of minute ventilation which would have enabled identification of any relationships which may have existed between mean ventilation and reductions in pulmonary function. Sly (1972) suggested that activities necessitating brief intervals of sustained exercise rather than prolonged exercise should be implemented in designing exercise programs for asthmatics. Sly's research (1972) attempted to identify whether comparable volumes of ventilation and total mechanical work during intermittent and continuous exercise elicited a similar degree of

bronchoconstriction. Sly (1972) also investigated the concept of a threshold amount of ventilation which may exist for the provocation of EIA. Due to the limited research conducted on young asthmatic subjects performing intermittent exercise, there is a strong need to investigate the ventilation volumes throughout intermittent exercise as well as measuring respiratory responses following exercise. Study two will enable a further insight as to whether intermittent exercise can cause a bronchodilatory response or EIA.

Purpose

To examine the influence of repetitive, high intensity work (6 minute duration) on the post exercise respiratory responses on children with exercise induced asthma.

Methods

Ten active asthmatics (five male and five female) with a mean age of 11.1 $\pm$ 0.2 years and eight active non-asthmatics (five male and three female) with a mean age 10.9 $\pm$ 0.2 years from local schools volunteered to participate in this study. Informed consent was obtained from the subjects and parents/guardians which was in accordance with the guidelines established by the Ethics Committee from the Royal Children's Hospital and the University. A respiratory questionnaire was attached with the consent form which consisted of 14 questions in relation to respiratory symptoms that required the parent/guardian to fully complete (Appendix A4). A similar respiratory questionnaire has been implemented previously (Riedler et al. 1994, Robertson et al., 1991). The questionnaire provided an initial screening of the subjects and addressed respiratory symptom questions which were suggestive of asthma. From the questionnaires responses those subjects who reported respiratory symptoms of asthma were invited to participate in the study.

The criteria for the asthmatic subject's inclusion in the study were: (i) displaying asthmatic symptoms through the respiratory symptoms survey, (ii) testing positive to the exercise challenge test, which was defined as a decrease in FEV_1 greater than 20% post exercise, (iii) being physically active as defined as regular participation in school PE classes and at least two other weekly sessions of organised sporting participation and (iv) being aged between 10 and 12 years. The maturational assessment was determined using the Tanner scale (1-5) for pubertal status. This involved the subjects making a private assessment of their maturation status by matching their perceived stage of development with one of the five sequential maturational stages presented to them in a pictorial form (Appendix B).

All asthmatic subjects withheld β_2-agonist or asthmatic medication therapy for 8 hours prior to all tests. None of the subjects were using inhaled steroids. Subjects who had significant decrease in lung function and who requested medication post exercise, were administered with a β_2 -agonist (salbutamol, 2 x 100μg) via a spacer (Volumatic™) (Glaxo Group Research, UK). Once the metered dose inhaler (MDI) was activated the subject was immediately asked to fully inhale and hold his breath for 10 seconds before slowly exhaling. The study involved the subjects attending the laboratory on five occasions over a two week period with all tests being performed in the morning. All tests were conducted in the laboratory with the environmental conditions remaining stable, the water content of the inspired air was < 10 $mgH_2O.L^{-1}$ (mean=8.04 ± 0.26 $mgH_2O.L^{-1}$), mean dry temperature was 20.7°C (±0.38), and the mean wet bulb temperature 14.4°C (±0.3) For the subjects to qualify for subsequent exercise testing, each subject's pre-FEV_1 values had to be greater than 75% of the predicted value (Polgar) and within 10% of the usual value. For all lung function tests, a Vitalograph (compact spirometer #42.00) was used with the subject standing and without a noseclip.

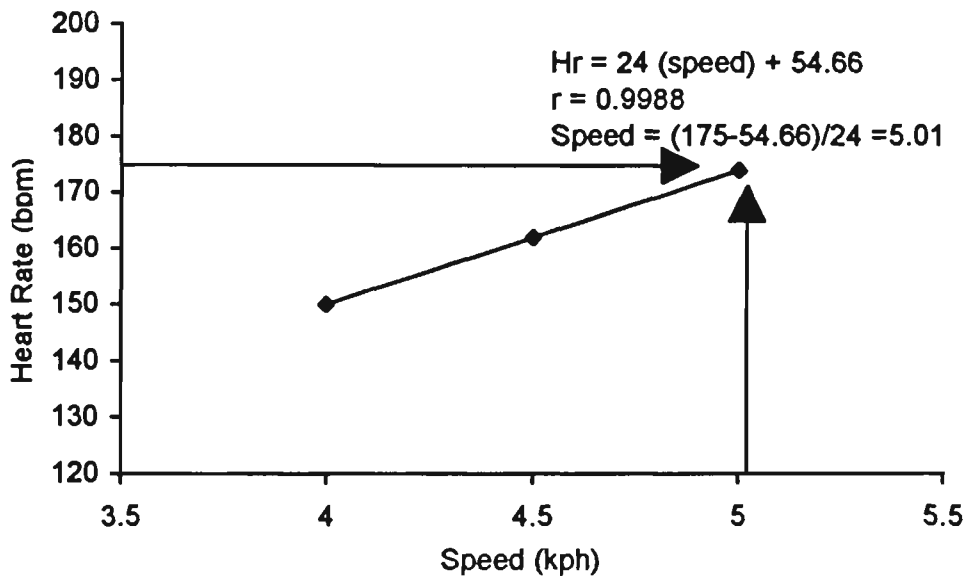
Subjects were instructed to inhale deeply and then to exhale as hard and as fast as they could. If there was a difference of more than 200ml between the duplicate FEV_1 values, then a third measurement was performed and subsequently the best of these two or three values was selected. Prior to any exercise tests the subjects were requested not to participate in any form of physical activity for four hours, nor ingest any food for at least two hours prior to testing. A 10 minute period of specific stretching exercises was performed prior to all exercise tests. This warm-up protocol was used in preference to aerobic low intensity warm-up because it may have influenced the sympathoadrenal responses. The major muscle groups were stretched for a period of 20-30s for two sets of each exercise. The stretching exercises comprised; lower back and hip stretch, hamstring stretch, quadriceps stretch, groin stretch and a calf stretch. These exercises were demonstrated to all subjects to ensure correct technique was performed (see Appendix C).

The determination of metabolic data was performed by using a Jaeger Oxycon open circuit metabolic system. It has been demonstrated by Reybrouck et al. (1992) that a breath-by-breath method for measuring respiratory values can be applied in children with an acceptable degree of validity and reproducibility.

This system has been previously detailed in Chapter Three. A peak $\dot{V}O_2$ / exercise challenge test was used to diagnose EIA and was utilised to determine the individual heart rate and running speed relationship. The exercise protocol required the subjects to run on a motorised treadmill at a set grade of 15% with the initial speed set at 4 kph for three minutes. The speed was subsequently increased 0.5 kph every 3 minutes. Following nine minutes of running, the speed was increased by 0.5 kph every minute until volitional fatigue. Subsequently, a linear regression analysis was calculated from the steady state heart

rates which were obtained from the submaximal running speeds during the peak $\dot{V}O_2$ test. From this regression workloads were predicted which would elicit heart rates of approximately 175 bmp (Figure 5.0). Heart rates were monitored via a Polar Sports Tester PE4000 (Polar Electro™, Hakamaantie, Finland).

Figure 5.0 Prediction of Workload from Heart rate

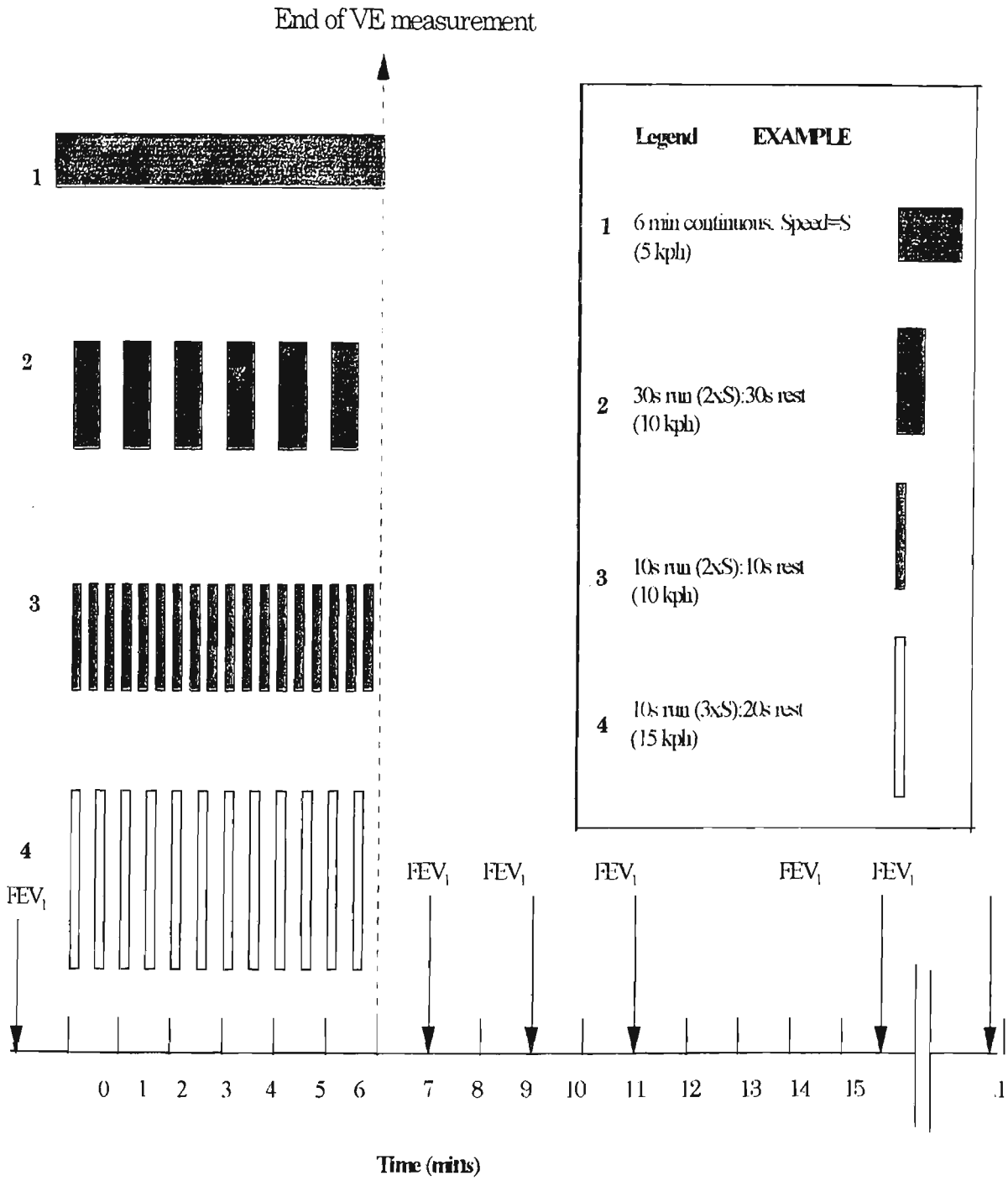


The aim of the peak $\dot{V}O_2$ test was to achieve a mean ventilation for six minutes above 60% of predicted Maximal Voluntary Ventilation [MVV = predicted FEV_1 x 35 (Jones, 1982)] as this is the standard criteria for reaching the desired ventilation in an exercise challenge test (Eggleston and Guerrant, 1976). The subjects were invited to attend the laboratory on another four separate occasions within a two week period, where they completed on each occasion a total of six minutes of exercise. Each test was designed to be of equal total work and equal ventilatory stimulus (HR 175 bpm, V_E 60% MVV for 4-5 min).

- The four different exercise regimens. (Fig. 5.1) were randomly applied to the subjects.
- V_E was averaged over the whole 6 min period of each test - including the rest period at the end of the intermittent tests.

Measurements of FEV_1 were taken pre exercise and at prior to exercise and during the recovery intervals of 1, 3, 5, 10 and 15 min.

Fig 5.1: Exercise Test Regimen Protocols



Data were statistically treated using independent t-tests for mean differences in descriptive data. One-way ANOVAs were used to determine group differences in performance data during peak $\dot{V}O_2$ test including V_E, $\dot{V}O_2$, heart rate, RER, % fall index of FEV_1 and rating of perceived exertion (RPE). A 2 X 4 ANOVA was used for the interaction between the two conditions (asthmatics and non-asthmatics) and the four exercise protocols. Where significant differences existed, Newman-Keuls post hoc analysis tests were applied. The 0.05 level of significance was adopted for all testing.

Results

Descriptive data for the two conditions are presented in Table 5.0. No significant differences existed in the physical characteristics between the asthmatics and non-asthmatics subjects (Appendix E2.1). The maximal effort profiles of the subjects are presented in Table 5.1 and show no significant difference in values for peak VO_2 expressed in $ml.kg^{-1}.min^{-1}$, maximal heart rate, mean V_E and RER. The results from the peak VO_2 test indicate that all subjects achieved mean maximal heart rates which exceeded 95% of the age predicted maximum and also attained an RER in excess of 1.05 at peak VO_2. This indicates that at least two of the peak VO_2 test criteria were achieved as described by Zwiren, (1989). The criteria for achieving an exercise challenge test was met by the asthmatic and non-asthmatic subjects achieving a mean ventilation greater than 60% of predicted MVV for four minutes (Figure 5.2). The mean ventilation during the peak VO_2 test for asthmatic and non-asthmatic subjects demonstrated no significant difference and the mean values were 46.62 and 45.38 $l.min^{-1}$, respectively (Figure 5.2). The asthmatic subjects were diagnosed positively from the peak VO_2 test demonstrating a significant percent reduction in FEV_1 values. The asthmatic and non-asthmatic subjects mean percent reduction in FEV_1 values following the peak VO_2 test revealed significant difference and the values were 32.90 and 1.38%, respectively (Figure 5.3).

No significant differences were reported between asthmatics and non-asthmatics for the mean VO_2, V_E, RER, and heart rate during the four exercise protocols (Table 5.2). There was no significant difference in the mean VO_2 in $ml.kg^{-1}.min^{-1}$ for the four exercise protocols between asthmatics and non-asthmatics indicating that the metabolic work was well equated in the four exercise tests (Figure 5.4). The collapsed mean VO_2 ($ml.kg^{-1}.min^{-1}$) values for asthmatic and non-asthmatic subjects during the continuous, 30 x 30s, 10 x 10s, and 10 x 20s protocols were 39.01, 39.38, 39.39 and 37.94 $ml.kg^{-1}.min^{-1}$, respectively. The mean ventilation for the six minute duration of each exercise protocol did not display any differences between the groups and exercise protocols. The asthmatic subjects mean ventilation for the four exercise

protocols ranged from 39.57 to 45.28l.min^{-1}. The non-asthmatic subjects mean ventilation for the four exercise protocols ranged from 41.95 to 46.01 l.min^{-1}. The mean ventilation from all the exercise protocols exceeded 60% of each subject's predicted MVV (Figure 5.5). The mean 60% predicted MVV for asthmatic and non-asthmatic subjects was 39.41 l.min^{-1}.

No significant differences were reported between asthmatic and non-asthmatic subjects for the mean heart rates during the exercise protocols (Appendix E2.2). The mean heart rates during the exercise protocols for asthmatic and non-asthmatic subjects exceeded 80% of percentage max heart rate and ranged from 83 to 88% max heart rate (Figure 5.6). Figure 5.7 represents the mean maximal percentage fall in FEV_1 for the four different exercise protocols. The mean maximal percentage fall in FEV_1 following the exercise protocols showed significant differences between asthmatics and non-asthmatics. Newman Keuls post-hoc analysis indicated significant differences in percentage reduction in FEV_1 values within asthmatics for the 30 x 30s and 10 x 10s protocol ($P<0.0001$). The interpretation of results may be however limited by low effect size for the continuous and the 30 x 30s protocol, and the 10 x 10s and 10 x 20s protocol ($d = .30$ and $d = .52$, respectively). The non-asthmatic subjects had no significant change in FEV_1 values following any of the four exercise protocols. The percentage reduction in FEV_1 values for the four exercise protocols for the asthmatics exceeded 20%. The asthmatic subjects mean percentage reduction in FEV_1 values ranged from 20 to 34 %. There were no differences between the RPE for breathing and local muscular fatigue in the legs between the four exercise protocols (Table 5.3). The responses from the Respiratory Symptoms Survey displayed the positive answers which are characteristic of asthma. From the 10 asthmatic surveys all of the replies indicated yes to questions 1, 2, 3, 4, 7 and 10 (Table 5.4).

Table 5.0: Descriptive characteristics of subjects in Study 2

Condition	Age (yr)	Mass (kg)	Height (cm)	BMI (kg/m^2)	Tanner (1-5)
Asthmatic	11.06	38.09	144.8	18.1	1.4
	(0.20)	(1.60)	(2.4)	(0.2)	(0.2)
Non-asthmatic	10.86	38.35	143.8	18.6	1.4
	(0.20)	(2.60)	(1.8)	(1.3)	(0.2)

M±SEM

Table 5.1 Maximal effort profile for asthmatic and non-asthmatic subjects

Maximal Effort Profile

Variables	A	NA
VO_2 Peak	57.24	54.44
($ml.kg^{-1} min^{-1}$)	(1.40)	(2.60)
V_E mean	46.61	45.37
($l. min^{-1}$)	(1.30)	(1.60)
RER	1.11	1.12
	(0.01)	(0.01)
Heart rate	206	205
(bpm)	(1)	(2)

M±SEM RER = Respiratory Exchange Ratio

A= asthmatics

NA= non-asthmatics

Table 5.2 Mean physiological measurements during the four exercise protocols

	Continuous		30x30s		10x10s		10x20s	
Data	A	NA	A	NA	A	NA	A	NA
VO_2	37.31	40.71	37.85	40.95	37.99	40.76	37.37	38.52
($ml.kg^{-1}.min^{-1}$)	±0.9	±1.8	±1.2	±1.6	±1.0	±1.6	±0.9	±1.0
V_E	39.57	41.95	45.43	44.40	43.52	45.77	45.28	46.01
($l.\ min^{-1}$)	±1.8	±2.0	±2.2	±1.9	±1.7	±1.42	±2.3	±1.3
Heart rate	175.7	178.1	180.8	182.4	178.6	181.6	181.5	185.0
(bpm)	±2.5	±2.0	±2.4	±2.6	±2.0	±2.0	±2.3	±2.6

A= asthmatics

NA= non-asthmatics

M±SEM

Table 5.3 Mean ratings of perceived exertion for the four exercise protocols on breathing effect and local muscular fatigue.

Protocol & measure	Asthamtic	Non-asthmatic
Continuous		
Breathing	4.04 (0.68)	3.87 (0.29)
Local muscular fatigue	4.75 (0.41)	5.37 (0.56)
30 x 30		
Breathing	5.50 (0.93)	4.87 (0.87)
Local muscular fatigue	5.30 (0.36)	5.12 (0.39)
10 x 10		
Breathing	4.50 (0.67)	4.62 (0.67)
Local muscular fatigue	5.10 (0.54)	5.62 (0.26)
10 x 20		
Breathing	5.7 (0.61)	4.87 (0.64)
Local muscular fatigue	6.05 (0.24)	5.62 (0.37)

M(±SEM) (Borg scale 1-10)

A= asthmatics

NA= non-asthmatics

Table 5.4 Responses of the Respiratory Symptoms Survey from the asthmatic subjects

Respiratory Symptoms Survey Questions	Yes	No	Don't Know
1. Has your child had wheezing or whistling in the chest at any time in the past?	10		
2. Has your child ever had asthma?	10		
3. In the last 12 months, has your child had a wheezing or asthma attack?	10		
4. In the last 12 months, how frequent were the wheezing or asthma attacks?			
None in the last 12 month			
Less than 4 attacks	1		
4 to 12 attacks	7		
More than 12 attacks	2		
5. In the last 12 months, has any wheezing or asthma attack woken your child at night?	7	2	1
6. In the last 12 months, has any wheezing or asthma attack been severe enough to limit speech to only one or two words at a time between breaths?	5	2	3
7. In the last 12 months, has your child sounded wheezy during or after exercise?	10		
8. In the last 12 months, has your child had a dry cough at night?	5	1	4
9. In the last 12 months, has your child usually brought up any phlegm or mucous from the chest first thing in the morning?	5	4	1
10. In the last 12 months, has your child woken with feeling of tightness in the chest first thing in the morning?	7	1	2
11. In the last 12 months, has your child had tightness in the chest or become short of breath when near animals, feathers or dust?	3	5	2
12. In the last 12 months, has your child been treated at any time with any of the following medications? Ventolin, Bricanyl, Nuelin, Somophyllin, Respolin, Berotec, Theodor, Elixophyllin	10		
13. Has your child ever suffered from bronchitis?	6	4	
14. Has your child ever suffered from wheezing with bronchitis or with a cold?	7	3	

Figure 5.2

Mean $\dot{V}_E$ for peak $\dot{V}O_2$ test for asthmatics and non-asthmatics

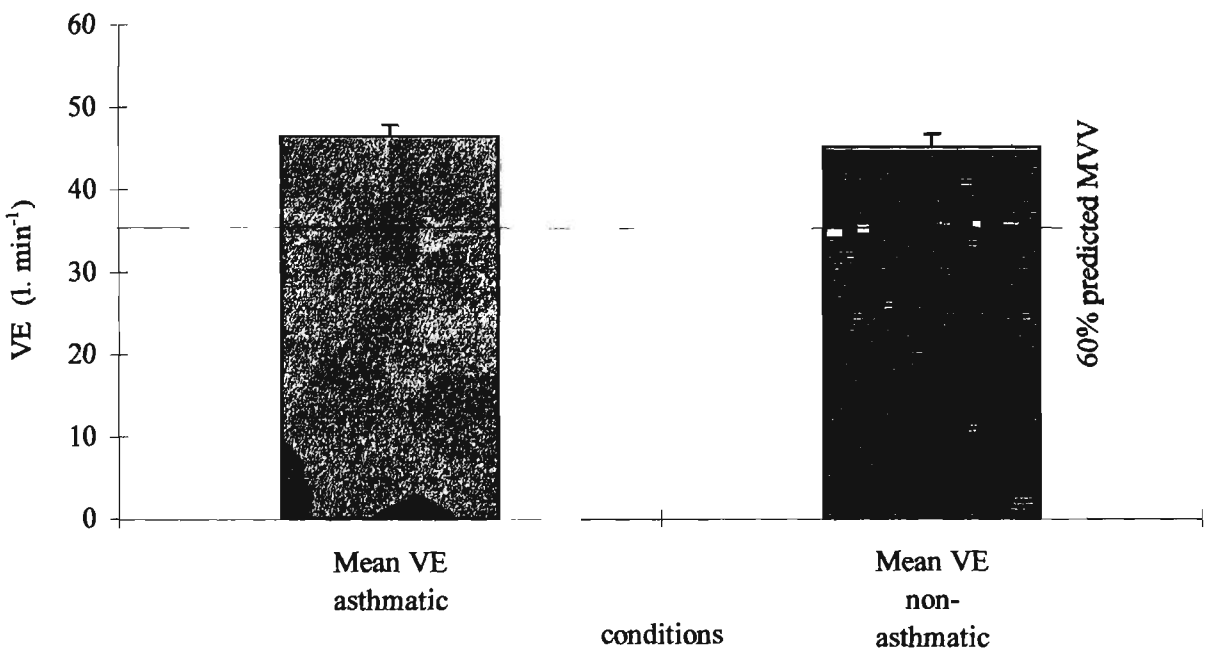
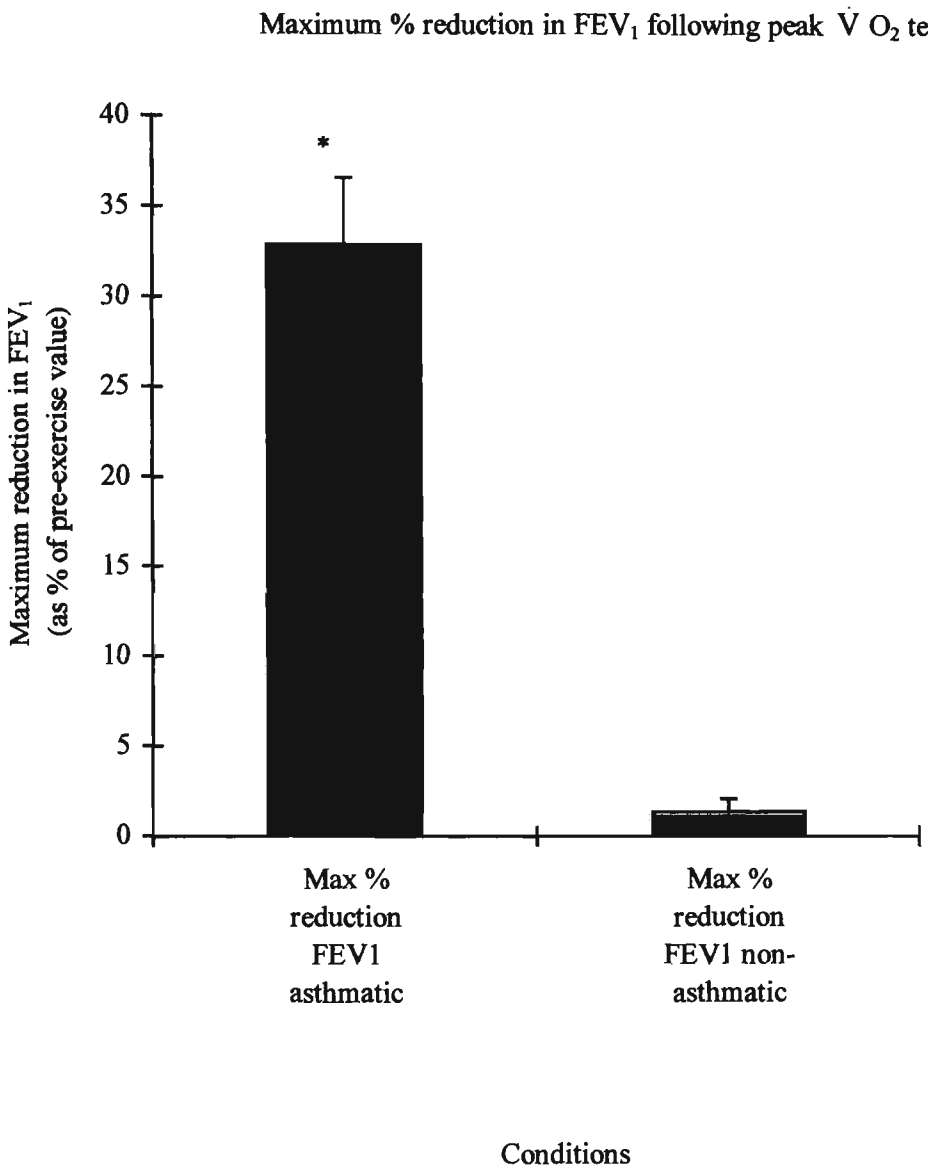


Figure 5.3



* P<0.05

Figure 5.4

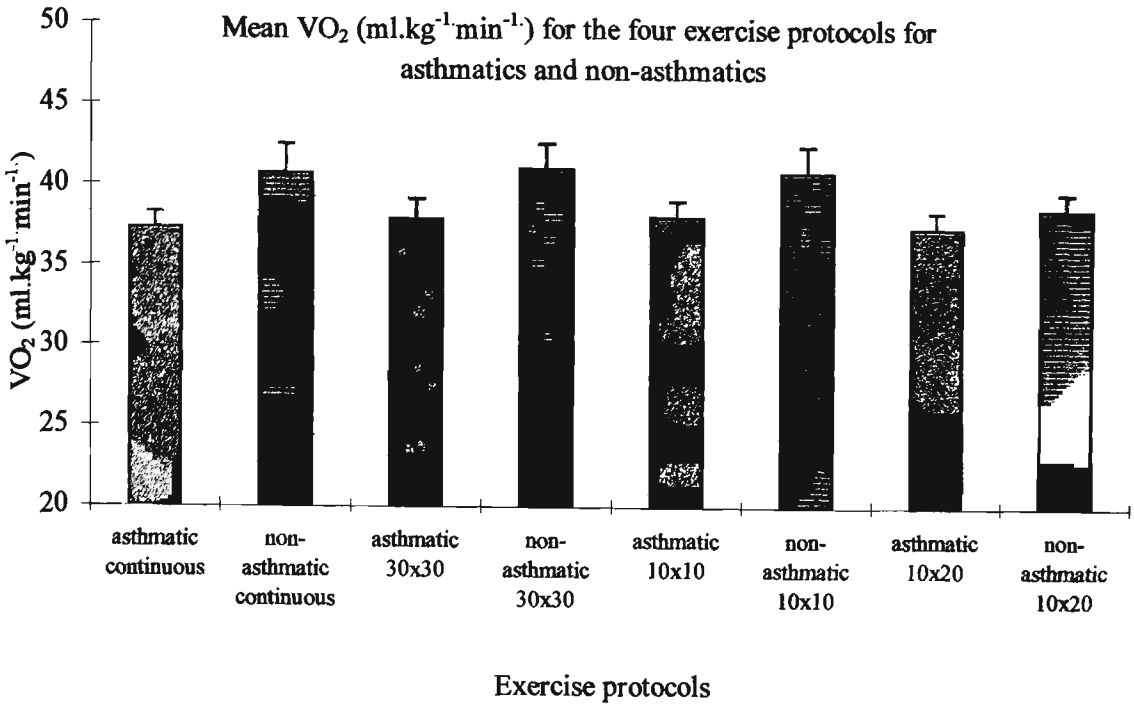


Figure 5.5

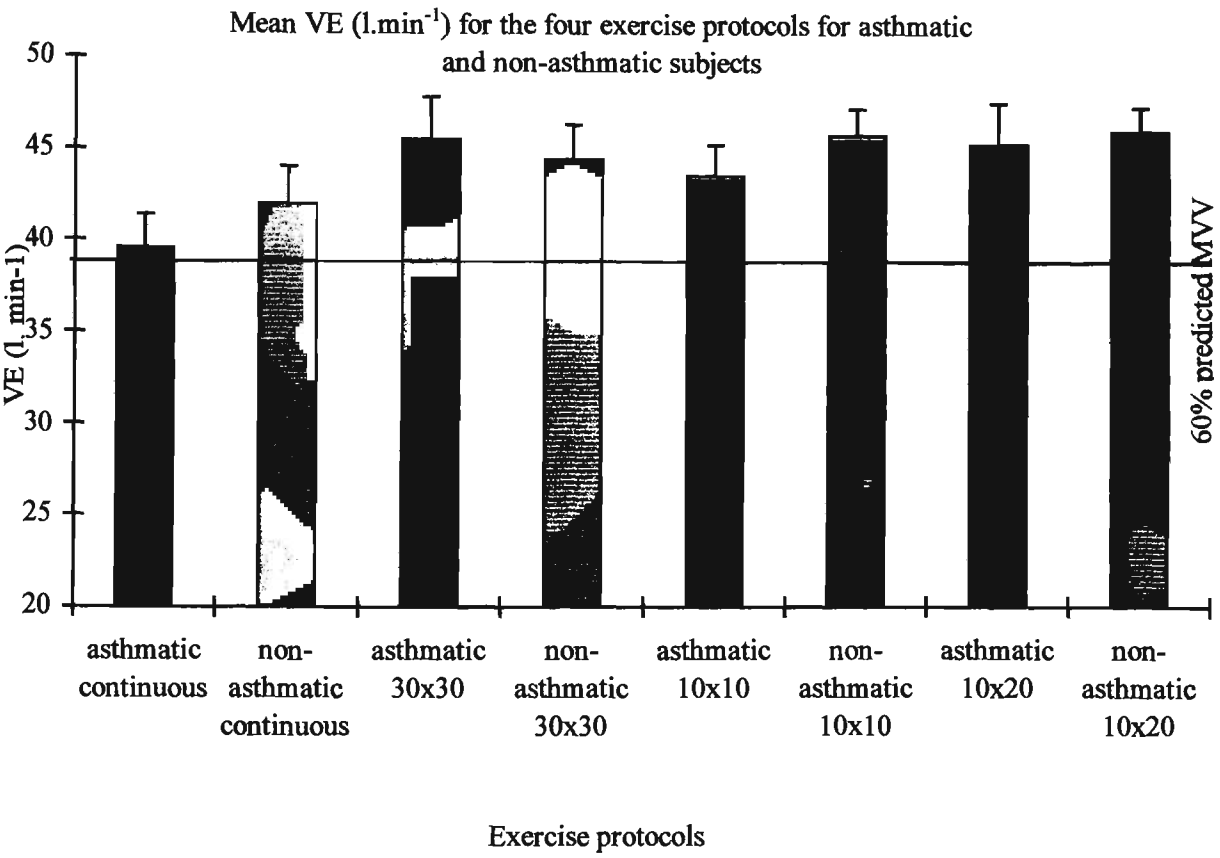


Figure 5.6

Mean heart rate for the four exercise protocols for asthmatics and non-asthmatics

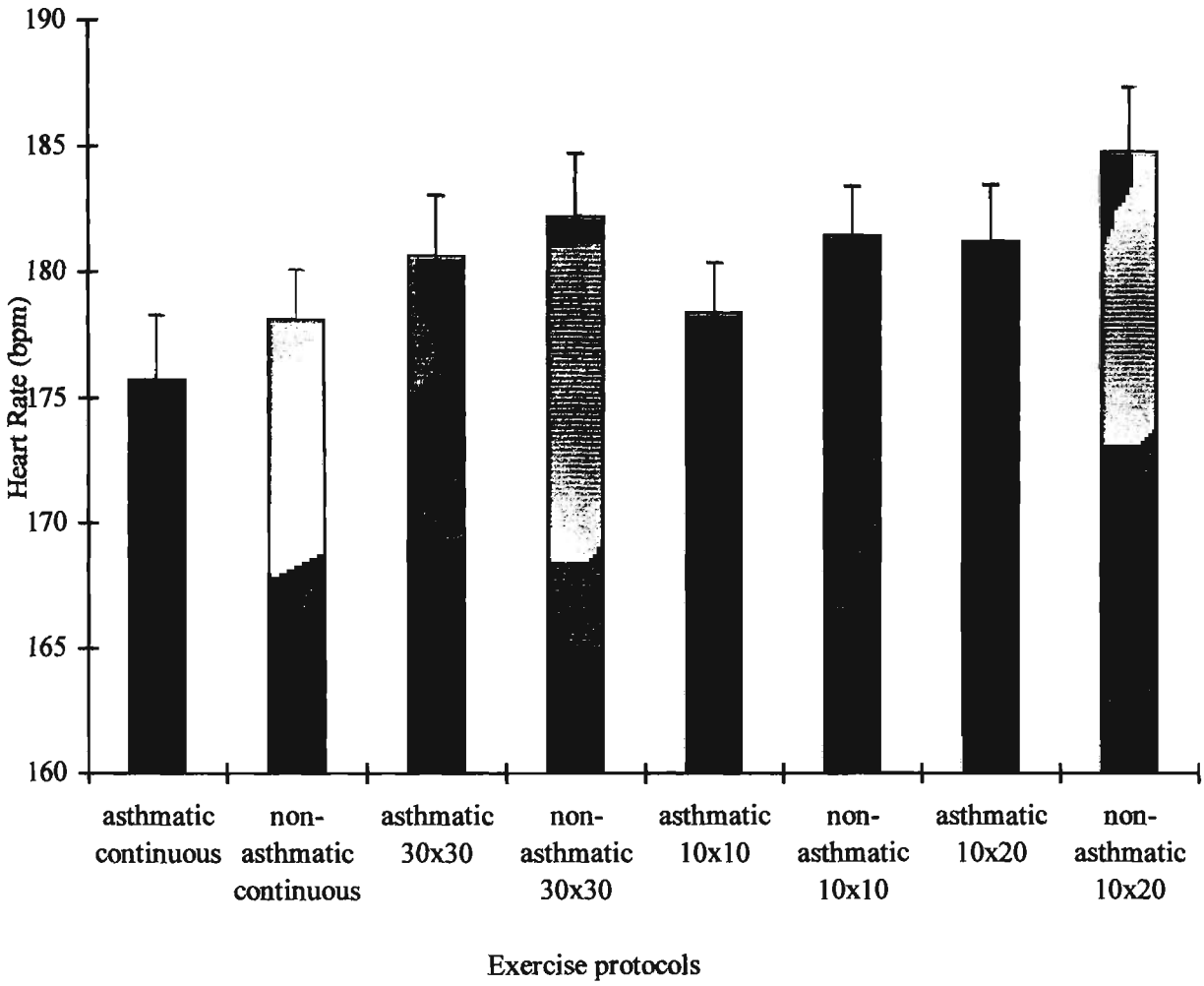
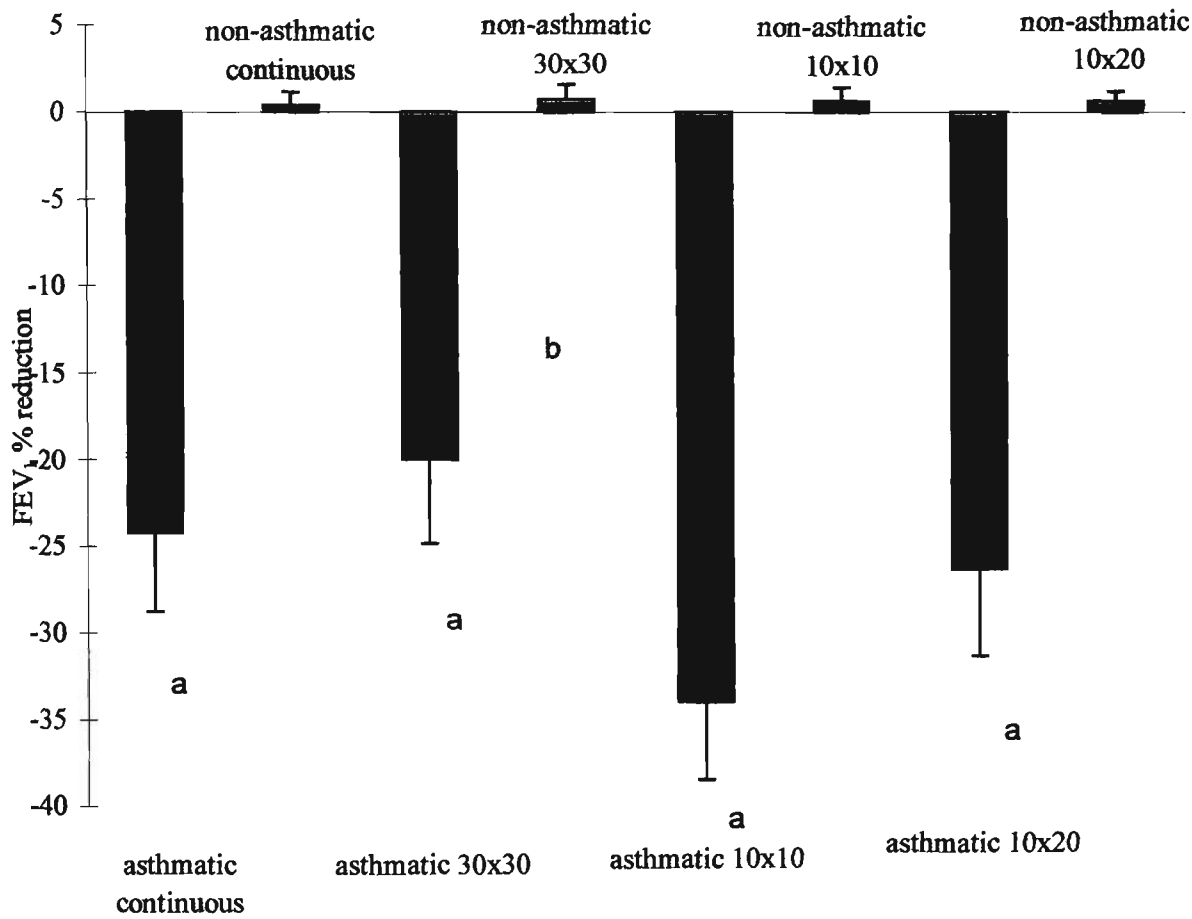


Figure 5.7

Mean % FEV_1 reduction for the four exercise protocols for the asthmatics and non-asthmatics



a denotes significant difference between asthmatic and non-asthmatics $P<0.05$

b denotes significant difference between the 30 x 30s and 10 x 10s protocol.

Discussion

The peak VO_2 test was critical to determine whether the subjects were diagnosed positively with EIA. This was reflective in the maximum % reduction in the FEV_1 values following the peak VO_2 test (Figure 5.3). The test enabled calculations of predicted workloads equivalent of 85% of maximal heart rate (Figure 5.0). The four exercise protocols were performed within the same total time period and displayed similar mean ventilations (Figure 5.5), mean VO_2 (Figure 5.4), and heart rates (Figure 5.6). The mean VO_2 for each test displayed strong similarities, therefore indicating that the metabolic work was well matched in each protocol. The standard criteria for reaching the desired ventilation in an exercise challenge test involved sustaining 60% of predicted MVV for four minutes (Jones, 1982). This was achieved in the peak VO_2 test (Figure 5.5) and all the exercise protocols.

A study performed by Anderson et al. (1972) on five asthmatic subjects aged between 25-30 years found that running elicited more severe bronchoconstriction than cycling. The authors noted however that the ventilation was generally greater during the bicycle exercise. All asthmatic subjects within this study demonstrated a significant decrease in $\%FEV_1$ following both exercise protocols. Reduction in FEV_1 during the investigation was recorded as the lowest FEV_1 post exercise value observed. For some of the asthmatic subjects, the true value for % FEV_1 reduction may not however have been reported. Requests for β_2-agonist medication from these subjects may prevailed researchers from measuring the maximal value for the % FEV_1 reduction.

The RPE was used as a subjective indicator of a psychophysical rating scale post exercise. It has been previously shown that asthmatics have a higher rated perceived exertion compared with non-asthmatics at similar heart rates and ventilation rates (Eakin et al., 1992, Yorio, 1992). The findings however from the present study showed no differences in the mean values for RPE between asthmatics and non-asthmatics following the four exercise protocols.

The uniqueness of the present study was the attempt to examine high intensity intermittent exercise. The protocol adopted in this study incorporated speeds which doubled the continuous workload and tripled the continuous workload. Previous studies which examined the responses from intermittent exercise involved speeds that were never more than 75% greater than the continuous speed (de Bisschop et al., 1992, McKenzie et al., 1994, Morton et al., 1982, Schnall and Landau 1980). Studies by Schnall and Landau (1980) and de Bisschop et al. (1992) involved testing asthmatics during bouts of short term exercise. The intensity of the tests imposed by the aforementioned authors could not be described as truly challenging anaerobic pathways. It could be argued that the protocol for exercise tests employed by previous studies were not pertinent to the typical intermittent activities of children. The typical activities of children or the team sports characteristic of intermittent exercise comprises greater dependence on anaerobic metabolism.

Morton et al. (1982) recognised the limitations in previous studies which attempted to provoke EIA in subjects with protocols involving continuous and intermittent exercise. Morton and co-workers (1982) subsequently investigated the effects of intermittent exercise protocols which they believed were more pertinent to "realistic" activity patterns. They adopted a work rest ratio of 1:3 imposing workload intensities equivalent to 175% of the speed selected for a continuous test. The authors (1982) reported significantly less airway obstruction following the intermittent protocols when compared to the continuous test. The intermittent protocols which produced the greatest airway obstruction were those with the highest intensities and shortest rest periods.

In the present study there were significant reductions in the asthmatic subjects' FEV_1 values following all four exercise protocols. The exercise protocol that had the greatest %FEV_1 reduction was the 10 x 10s bout and the least %FEV_1 reduction occurred following the 30 x 30s protocol (Figure 5.7). There was no clear relationship between the ventilation and the % FEV_1 reduction (Figure 5.5 and Figure 5.7). It was postulated by Godfrey (1992), that EIA is triggered by an increase in ventilation thus producing the cooling and drying of the airways. He further contended that this trigger liberates the mediators which act on the airways and thus resulted in bronchospasm. McFadden (1985) reported that high ventilation with a combination of a low temperature of inspired air pushes the conditioning process from the upper to the lower airway. This subsequently causes movement of heat and water from the mucosa and results in a greater quantity of thermal energy needing to be transferred. The cooler the airways become, the quicker they rewarm and the greater the narrowing of the bronchi (McFadden 1985). McFadden's theory was later challenged by Anderson (1988), who reported that an increase in ventilation initiates evaporation of mucosal surface water which also increases osmolarity, causes mast-cell degranulation and constriction of airway smooth muscle.

The focus of this study however was not to identify which of these mechanisms of EIA transpire but to investigate whether intermittent exercise is as effective as continuous exercise in provoking EIA. There is no doubt that the intermittent exercise bouts exceeded a "critical" threshold which initiated the mechanisms of EIA and all conditions produced significant falls in FEV_1. It is difficult to ascertain why the mean ventilation of the exercise protocol for the 30 x 30s test displayed the highest V_E and subsequently displayed the lowest %FEV_1 reduction in the asthmatic group. With the mean V_E exceeding the predicted 60% MVV it would be expected to display greater % FEV_1 reductions. According to McFadden and Gilbert (1994),when V_E increases, the severity of obstruction increases. An exception to this trend occurs when respiratory thermal fluxes are prevented, such as when fully humidified air (37°C) is inhaled. The environmental conditions in the present study remained constant throughout the testing and the water content of the inspired air was less 10 $mgH_2O.L^{-1}$. Alternatively the work of Anderson and

Smith (1988), reported that the stimulus for EIA is the loss of water from the intrathoracic airways while they are bringing large volumes of air to alveolar conditions in a short period. The two possible mechanism presented by McFadden (1985) and Anderson (1988) should be applicable to the relationship between V_E and % FEV_1 reductions, but this was not evident in the 30 x 30s test.

Schnall and Landau 1980, postulated that the repeated short runs may elevate circulating catecholamines or alter vagal-sympathetic balance. It is difficult to explain why the 30 x 30s protocol displayed the smallest %FEV_1 reduction and the highest mean V_E. It has been shown that high intensity work correlates with high levels of catecholamines (Lehmann et al., 1981). The 10 x 20s protocol had the greatest %FEV_1 reduction when compared to the 30 x 30s test. The 30 x 30s test also involved a greater anaerobic contribution and subsequently may have had elevated circulating catecholamine levels. In theory this should have provided a defence against bronchoconstrictor influences. If there was an increase in catecholamines during the test this may explain why the FEV_1 values were the lowest compared to the other protocols. Exercise elevates catecholamine levels (Pichurko et al., 1986). There is some evidence to suggest however, that there are blunted levels of circulating catecholamines following exercise in asthmatics compared with normals (Barnes et al., 1981, Warren et al., 1982). This may also add to the conjecture as to why there was no bronchodilation present following any of the high intensity intermittent exercise tests in the asthmatic subjects. It has also been established that repeated exercise can diminish the post exercise increase in airway resistance and promote a refractory period (de Bisschop et al., 1992, Nowak et al., 1992). This however did not occur. It has been suggested that the depletion of mast cell mediator stores is responsible for the refractory period (Ben-Dov et al., 1983, Nowak et al., 1992). This theory has been opposed by Jarjour et al. (1992) who postulated that EIA was not associated with mast cell mediator release or increased inflammatory cells in the air space. From their findings Jarjour et al. (1992) concluded that the release of mediators from pulmonary mast cells may not play an important part in the pathogenesis of EIA. The exact mechanisms which can fully explain refractoriness and bronchodilation following exercise are still unclear. Warren et al. (1984) suggested that bronchodilation during exercise is most likely to be due to the reduction in vagal tone rather than an effect of circulating catecholamines. Mechanisms for the valid measurement of vagal tone remain controversial.

In the present study it was expected that the high intensity bouts of exercise would increase the sympathoadrenal response and subsequently increase bronchodilation or even attenuate the potential EIA provocation. There is little evidence to support this theory and there are no findings from studies on asthmatic children studying circulating catecholamines following high intensity exercise. From the data it is evident that the mean minute ventilation, heart rate, metabolic and mechanical work remained constant

throughout the four exercise tests. The %FEV_1 reduction values for the four separate protocols were all greater than 20% which demonstrates that high intensity intermittent exercise is just as potent in causing EIA as is continuous exercise. This finding may challenge other previously published results (Edmunds et al., 1978, Eggleston et al., 1976, Godfrey 1975, Jones et al., 1963, McKenzie et al., 1994, Morton et al., 1982, Wilson & Evans 1981).

A combination of factors may exist to explain why no bronchodilation was evident in the asthmatics following any of the high intensity intermittent exercise tests. The reduced sympathoadrenal response to exercise in asthmatics with EIA may play an important role in the pathogenesis of bronchoconstriction by a permissive action on the mast cell (Barnes et al., 1981). The difference in the relationship between non-asthmatics and asthmatic subjects sympathoadrenal responses following exercise remains controversial. Berg and Keul (1988) reported suppressed catecholamine levels (17%) in younger subjects when compared with older subjects. The results of previous studies may be compounded by an age related attenuation of catecholamine response to exercise in young populations. This obviates the need for further investigations of the role of circulating catecholamines in young asthmatic and non-asthmatic subjects following high intensity intermittent exercise.

Chapter Six

Study Three

An Investigation of the Physiological Responses of Asthmatic Adolescents to a Number of Different Short Term High Intensity Exercise Bouts (less than 60 seconds).

An Investigation of the Physiological Responses of Asthmatic Adolescents to a Number of Different Short Term High Intensity Exercise Bouts (less than 60 seconds).

Abstract

The purpose of this study was to investigate the physiological and anaerobic responses of adolescent males to high intensity exercise of short duration. Ten healthy and active asthmatic adolescents (mean age 15.0 years) were compared with eleven healthy and active non asthmatics (mean age 14.5 years). Maturational status was determined by salivary testosterone in asthmatic and non-asthmatic males (means, 179.6 ρM, 184.2 ρM, respectively) and Tanner scale for pubertal development (means, 4.05, 4.22 for asthmatics and non-asthmatics, respectively). Asthmatic subjects withheld medication for eight hours prior to any exercise tests. The diagnostic tool used for exercise-induced asthma (EIA) from a Peak VO_2 test from which subjects who demonstrated FEV_1 (forced expiratory volume in one second) value with a 15% or greater reduction from their pre-exercise FEV_1 were classified as having EIA. All tests were performed in a controlled environment denoted by a relative humidity set at 35% (± 3% relative humidity). The subjects were tested on three occasions on a cycle ergometer. The order of conduct of the three tests was randomised. The tests involved three varying "supramaximal" exercise time protocols with total workload being equated. These were workloads were: (i) a 1 x 30s "All-out" Wingate Test, (ii) a 2 x 15s Wingate Test and (iii) a 3 x 10s Wingate Test. Blood borne markers of exercise metabolism were also monitored from samples taken from a forearm vein following the insertion of a teflon catheter. These markers included plasma lactates, plasma adrenaline and nor-adrenaline, and measures of acid base regulation. The results revealed no differences in the percentage change in FEV_1 values between asthmatic and non-asthmatic subjects following the high intensity exercise tests. The anaerobic performances of peak and mean power also showed no differences between asthmatics and non-asthmatics. There were however, blunted adrenaline levels in asthmatic subjects following the 1 x 30s, 2 x15s, and 3 x10s All-out Wingate test at 1 minute following exercise. Mean adrenaline values were 1.55 and 3.89, 1.05 and 2.71, and 1.19 and 2.24 nmol/l for the aforementioned protocols in the asthmatics and non-asthmatics, respectively. There were also significantly lower plasma lactate values following the three different high intensity tests between asthmatics and non-asthmatics. The high intensity exercise tests involving short duration did not cause any FEV_1 reduction with the asthmatics. Overall the anaerobic performances of asthmatic and non-asthmatic adolescents elicited similar performance outcomes but appeared to differ in the blood borne markers of anaerobic adaptations. The findings of similar anaerobic performances from different metabolic adaptations may be related to the long term effects of medication in subjects with EIA tested in this study.

Introduction

Study two in this thesis demonstrated that high intensity exercise for a period of six minutes can provoke EIA, however there is uncertainty about the association between high intensity exercise involving short durations (less than 1 min) and the incidence of EIA in children. A study performed by Inbar et al. (1981) examined 10 asthmatics (mean age, of 32 years) which involved tests of short-exhaustive exercise treadmill running lasting between 40 -50 seconds. The authors (1981) measured a number of respiratory responses including; pre and post exercise forced vital capacity (FVC), forced expiratory volume at 1 second (FEV_1), mid-maximal expiratory flow (MMEF), airway resistance (R_{aw}), thoracic gas volume (TGV), specific conductance (Sg_{aw}) and V_E BTPS. Arterial blood samples were measured for pH and lactic acid concentrations. The short duration of supramaximal treadmill running for less than 1 minute, caused a drastic fall in MMEF, however, demonstrated no significant changes in FEV_1 or R_{aw}. It was postulated that the short-exhaustive exercise performed may have served as a simple and accurate stimulus for detecting small airway obstruction as measured by the MMEF. It was also postulated that exercise of shorter duration than two minutes usually fails to cause large airway obstruction. There were no measurements of blood borne indices of the sympathoadrenal responses often associated with high intensity activity (Kjaer et al., 1986), nor was a control group used to assess differences between asthmatics and non-asthmatics. Intermittent exercise (including repeated periods of maximal or high intensity effort) constitutes the physical activity of numerous people (Gaitanos et al., 1993). Repeated bouts of intermittent exercise are inherent in the spontaneous play of young people (Cooper, 1993) and in many of the popular sports selected in leisure time.

Intermittent activities may help to maintain elevated levels of circulating catecholamines released during exercise. It has been postulated that this may be the mechanism of the observed bronchodilator influence following exercise (Barnes, 1992 and Pichurko et al., 1986). Adreanline and nor-adrenaline are commonly accepted indices of sympathetic activity and can influence cardiocirculatory activity and metabolic reactions as well as playing a major role in brochodilation (Christensenet al., 1983, Galbo et al., 1975). It has been suggested that continued exercise stress in the form of either continuous exercise or intermittent exercise helps maintain circulating catecholamine levels which may contribute to running through the EIA phenomenon (Godfrey, 1974, Pichurko et al., 1986, Reiff et al., 1989 and Schnall Landau, 1980). It remains uncertain whether asthmatics have attenuated levels of circulating catecholamines following exercise. According to Barnes (1980), this impaired rise in circulating catecholamines may subsequently cause a more likely release of mediators. Barnes et al., (1981) tested 7 asthmatics (mean age 16.3 years) and 6 non-asthmatics (mean age 16.5 years) during a standard treadmill exercise test and then during isocapnic hyperventilation. Barnes et al, (1981) demonstrated that there were no differences between the maximum minute ventilation or heart rate increase during exercise in asthmatic and non-asthmatic

subjects. There were however, marked difference in catecholamine response. This reduced sympathoadrenal response to exercise in asthmatics was not explained. It was however suggested that circulating catecholamines may have no direct role in EIA but may play a role in the pathogenesis of bronchoconstriction by a permissive action on the mast cell. Chryssanthopoulos et al, (1978) tested 7 asthmatic (mean age 25.5 years) and 9 non-asthmatic (mean age 25.6 years) subjects during an incremental treadmill test. They reported that adrenergic response of the asthmatics did not differ from that of non-asthmatics. This finding was supported by Larsson et al, (1982) who also demonstrated that asthmatic subjects produced similar catecholamine levels to non-asthmatic subjects following exercise. The studies which have investigated catecholamine levels following exercise have not involved supramaximal workloads from young subjects. It has been shown that catecholamine levels increase rapidly with the onset of anaerobic metabolism (Brooks et al., 1990, Galbo et al., 1975, Gratas-Delamarche et al., 1994, Kjaer, M. 1989 and Warren and Dalton, 1983).

Much controversy surrounds discussions of catecholamine responses in asthmatics following exercise. The differences presented in previous studies in sympathoadrenal responses following exercise may be due to the subject variability and inconsistencies in the protocols employed across the studies. For example, the maturational status was not consistently determined either by Tanner scale or Salivary Testosterone in those studies using young populations. It is well documented that anaerobic metabolism and catecholamine levels increase concomitantly with pubertal growth (Bar-Or, 1983, Eriksson et al., 1972, Lehmann et al., 1981). Contrary to these findings Rowland et al., (1996) however, suggests that sympathetic responses throughout maximal and submaximal exercise are independent of biological maturation. There is limited available evidence to support an abnormal response in the catecholamines in asthmatics following exercise, particularly post supramaximal workloads. Supramaximal exercise is prevalent in the demands of many sport-based activities popular among young people in Australia. The suppressed catecholamine theory warrants further investigation and it would be specifically useful to examine responses of subjects with EIA following high intensity exercise of short duration.

Purpose

The purpose of this study was to investigate the physiological and anaerobic performance responses to different short term (less than 1 minute), high intensity exercise bouts in asthmatic and non-asthmatic adolescents.

Method

Ten asthmatic adolescent males (mean age 15.04 years) and eleven non-asthmatic males (mean age 14.53 years) from the one secondary school were recruited for the study. Subjects and parents provided written consent after being informed verbally and in writing of the experimental protocol. The protocol was reviewed and received the approval of the Human Research Ethics Committee of the University. The asthmatic subjects were provided with a respiratory questionnaire which was attached to the consent form. The questionnaire provided an initial screening of the subjects addressing respiratory symptom questions which were suggestive of asthma (see Appendix A3). From the responses to the questionnaires, those children who reported respiratory symptoms of asthma were invited to participate in the initial screening tests of the study.

The criteria for subjects selection into the asthma group were:

(i) displaying asthmatic symptoms through the respiratory symptoms survey

(ii) testing positive to the exercise challenge test, which was defined as a decrease in FEV_1 greater than 15% post exercise

(iii) being physically active (regular participation in school PE classes and at least two other weekly sessions of organised sporting participation)

(iv) being male between 13 to 16 years of age (Tanner Scale 3-5 for pubic hair and genital development)

Morphological characteristics and skinfold measurements (sum of six) taken according to Harrison et al. (1988) were determined on the first testing session shown in Table 6.0. The maturational status was examined by using two methods. The first method focused on the Tanner scale (1-5) which involved the subjects making a private self-assessment of their maturational status by matching their development with one of the five sequential maturational stages presented through photos (Appendix B). Salivary Testosterone samples provided a further means of maturational status. Saliva was collected on three consecutive mornings, it was then stored at -20°C until analysis. Salivary testosterone was analysed by a radio-immunology method which has been previously described (Chapter Three, pages 51-52).

The asthmatic subjects were requested to withhold β_2-agonist and any other asthmatic medication therapy for eight hours prior to all tests. There were no asthmatic subjects who were currently using inhaled steroids. When a subject experienced significant fall in lung function and requested medication, a β_2 -agonist (salbutamol, 2 x 100μg) via a spacer (Volumatic) (Glaxo Group Research™, UK) was provided. The study involved the subjects attending the laboratory on four separate occasions over a two week period. All tests were performed in the morning and were conducted in an environmental chamber (Tabai™) with the conditions remaining stable. The water content of the inspired air was < 9 $mgH_2O.L^{-1}$ (mean 5.4 ±0.04 $mgH_2O.L^{-1}$). The mean dry temperature was (13.5 ±0.05°C) and the mean wet bulb temperature was held constant at 8.0 ±0.05°C. For the subjects to qualify for subsequent exercise testing, each subject's pre- FEV_1 values had to be greater than 75% of the predicted value (Polgar, 1971) and within 10% of his baseline value. For all lung function tests a Welch Allyn (PneumoCheck™ Spirometer) was used with the subject standing without a noseclip. Prior to testing a three litre known volume syringe was used for calibration. Subjects were instructed to inhale deeply and then to exhale as hard and as fast as they could until full exhalation had been obtained. If there was a difference of more than 0.2 L between the duplicate FEV_1 values, a third measurement was performed and subsequently the highest values of these was recorded. Values for $FEF_{25-75\%}$ were obtained from a manoeuvre which meets the diagnostic FVC recommendations (American Thoracic Society, standardization of spirometry, 1994). Lung function tests were performed prior to the exercise and at the post exercise intervals of 1, 3, 5, 10 and 15 minutes (Figure 6.0). Prior to any exercise tests, the subjects were requested to refrain from any form of physical activity for twenty-four hours. They were also required to refrain from the ingestion of any food for at least two hours prior to testing.

For the purpose of multiple sampling of blood an indwelling catheter was inserted into the forearm vein of subjects while they were lying supine in a quiet room. A 20 minute rest period was provided to overcome the stress of the catherization. Baseline samples were collected before the warm-up protocol and additional samples were drawn at minutes 1, 3, 6, and 12 post exercise (Figure 6.0). All samples were drawn while the subject was in a supine position. The samples were then immediately placed on ice until analysed. The assays analysed within minutes of exercise cessation were blood gases, and acid-base measurements including PCO_2, PO_2, HCO_3, and pH. The assays which were treated and placed on ice for future analysis included plasma lactate and catecholamines. All blood assay procedures have been previously described in the general methods Chapter Three (pages 50-51).

Specific stretching exercises were performed prior to all exercise tests for a 10 minute period. This warm-up protocol was used in preference to an aerobic low intensity warm-up. Aerobic exercise may have influenced the physiological responses that may be associated with the high intensity exercise. The major muscle groups were stretched for a period of 20-30s for two sets of each exercise. The stretching exercises comprised of a lower back and hip stretch, a hamstring stretch, a quadriceps

stretch, a groin stretch and a calf stretch. These exercises were demonstrated to all subjects to ensure correct technique was performed (Appendix C).

An open-circuit metabolism technique was used to obtain metabolic measurements during the peak oxygen uptake test and the supramaximal tests. Ventilation was measured via a Pneumoscan ventilometer which was connected to a mixing chamber. Online metabolic and ventilatory determination has been previously described (Chapter Three). The heart rate was monitored with a Polar Sports Tester PE4000 (Polar Electro, Hakamaantie, Finland) throughout the exercise tests. EIA was diagnosed from an exercise challenge test which also elicited a peak $\dot{V}O_2$. The test elicited a natural stimulus of EIA for the asthmatics and provided the means to assess maximal work capacity and work tolerance. The criteria for the $\dot{V}O_2$ peak test was a heart rate exceeding 95% predicted maximum heart rate, an RER greater than 1.05, a plateau of oxygen consumption at high workloads of approximately within 2.0 $ml.kg^{-1}.min.^{-1}$ and or, an observation of apparent exhaustion (Zwiren, 1989). The exercise tests were performed on a Monark ™ 814 cycle ergometer. The exercise challenge test was modified so that a Peak VO_2 could be achieved. The cycling protocol consisted of the subjects maintaining 80 rpm throughout the test with the initial workload being 50 watts for the first two minutes. Following from this stage the watts were increased to the workload predicted to elicit 60% of predicted MVV(Maximum Voluntary Ventilation) [MVV = predicted FEV_1 x 35 (Jones, 1982)] for a further three minutes. At the completion of this stage there was a further increase of 25 watts imposed every minute until volitional exhaustion. Subjects' FEV_1 values had to have a 15% or greater reduction from their pre-exercise FEV_1 for them to be classified as having EIA (Anderson and Smith 1988).

Subjects were tested to a randomly ordered series of tests on a cycle ergometer. These tests involved three varying supramaximal exercise time protocols which were:

- a 1 x 30 s All out Wingate Anaerobic Test (WAnT)
- a 2 x 15 s Modfied All out WAnT
- a 3 x 10 s Modfied All out WAnT (Figure 6.0).

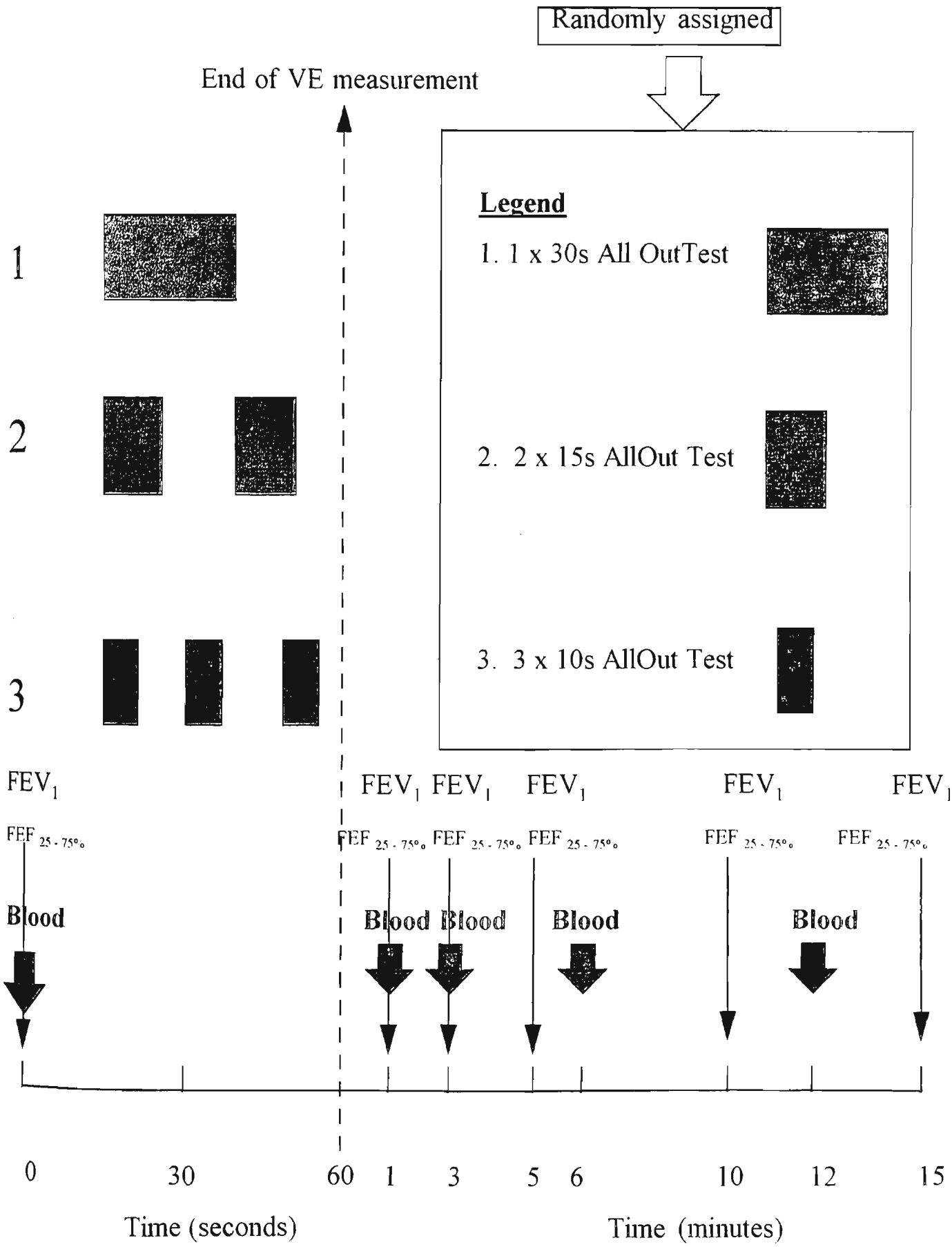
Subjects were required to pedal as fast as possible against a pre-determined resistance (0.075 $kp.kg^{-1}$BM) (Ayalon et al., 1974, Bar-Or, 1987).

Peak and mean power outputs from the modified WAnTs were obtained from the three tests. Peak power was defined as the highest mechanical power output in watts over a 5 s interval elicited within the 30 s period of work. Mean power was defined as the average mechanical output produced over the 30 s period work. Both mean and peak power were expressed in watts (w) and watts per kilogram of

body mass ($W.kg^{-1}$). At 15 s prior to the commencement of the test, a pre-set weighted basket was raised to reduce the tension of the band on the flywheel, and the subject began pedaling at 80 rpm against minimal resistance. On the command 'GO' the basket was lowered and the subject began sprinting maximally until they were given the command 'STOP'. During the trials involving repeated bout protocols the basket was raised until the next workload was imposed.

A series of 2 X 3 ANOVAs was used to determine any difference in performance data between the two groups and the three high intensity tests mean data (SPSS). A series of ANOVAs were conducted on the respiratory measures and blood analysis with pre and post exercise time being computed as repeated measures. Newman-Keuls post hoc analysis tests were applied wherever appropriate. The alpha level of $P<0.05$ was accepted as significant.

Figure 6.0 Exercise test protocol for the three high intensity tests



Results

There are a number of descriptive characteristics of the two groups in this study which demonstrate homogeneity with the sample populations. No significant differences were reported in any of the descriptive characteristics between asthmatic and non-asthmatic subjects (Table 6.0 and Appendix E3.1). There was a significant relationship between salivary testosterone and Tanner scale (r = 0.801) and between salivary testosterone and chronological age (r = 0.602) which are presented Figure 6.1, and Figure 6.2. Age and maturation correlated positively to salivary testosterone whereas the correlation was higher with the maturation than with chronological age. The maximal effort data presented in Table 6.1 demonstrates similarities in aerobic power of the asthmatic and non-asthmatic subjects. It reveals no significant differences between asthmatic and non-asthmatic males in relative and absolute peak $\dot{V}O_2$ ($ml.kg^{-1}.min^{-1}$ and $l.min^{-1}$), maximal heart rate and the RER value at max. The results from the $\dot{V}O_2$ peak test show that all subjects attained mean maximal heart rates which exceeded 95% of the age predicted maximum and also achieved an RER in excess of 1.05 at peak $\dot{V}O_2$. This indicates that at least two of the $\dot{V}O_2$ peak test criteria were achieved (Zwiren 1989).

All asthmatic subjects tested positively to the provocation test. The asthmatic subjects' peak reduction in FEV_1 responses ranged from 11.70 to 53.80 % and non-asthmatic subjects' peak reduction ranged from -1.23 to 7.59%. There were significant differences between asthmatics and non-asthmatics in the post exercise falls in respiratory function following the peak $\dot{V}O_2$ test. These mean values were 25.87% and 1.25% for the asthmatics and non-asthmatics, respectively (Figure 6.3 and Appendix E3.2). The mean ventilation for the last six minutes of the $\dot{V}O_2$ peak test exceeded each subject's predicted 60% MVV. This value reached the criteria for ventilation responses required for an exercise challenge test for eliciting EIA (Eggleston and Guerrant, 1976). Figure 6.4 displays the mean ventilations for the last 6 minutes of the $\dot{V}O_2$ peak test which were 90.71 and 92.34 $l.min^{-1}$ displaying no significant difference between asthmatic and non-asthmatic subjects respectively. Figure 6.4 also presents the subjects' mean predicted MVV which displayed no significant difference between asthmatic and non-asthmatic subjects. These were 119.04 and 128.40 $l.min^{-1}$ for the asthmatic and non-asthmatic subjects respectively.

The results of the anaerobic performances (peak and mean power) from the three high intensity tests elicited no differences among the test protocols and between asthmatics and non-asthmatics (Table 6.2

and Appendix E3.2-3.3). The peak power (watts) from the three high intensity tests (1x30s, 2x15s, 3x10s) for asthmatic subjects were 567.3, 569.8 and 559.4, respectively. The non-asthmatic peak power (watts) from the three high intensity tests were 589.9, 592.7 and 587.1, respectively. The mean power (watt), relative peak power ($w.kg^{-1}$) and relative mean power ($w.kg^{-1}$) for the three high intensity tests displayed no significant difference between asthmatic and non-asthmatic subjects (Table 6.2).

Presented in Figures 6.5 and 6.6 are the FEV_1 responses of asthmatic and non-asthmatic subjects following the high intensity tests. It was demonstrated that there were no significant reductions after any of the high intensity tests within the asthmatic subjects and there were no differences reported in the respiratory responses between asthmatic and non-asthmatic subjects ($P<0.28$) (Figure 6.5 and 6.6 and Appendix E3.2). Figure 6.7 displays evidence that there is a greater than 10% fall in $FEF_{25-75\%}$ for the three tests. This indicates that small airway obstruction occurred. The asthmatic $FEF_{25-75\%}$ values demonstrated a significant decline following the high intensity tests (1 x 30s, 2 x 15s, 3 x 10s) and these percentage reductions were 14.2, 16.15 and 13.64, respectively.

Table 6.3 presents the metabolic data which was collected the three intensity tests. There were no significant differences in the $\dot{V}O_2$ ($ml.kg^{-1}.min^{-1}$) elicited by the three tests and between the asthmatics and non-asthmatics. The mean $\dot{V}O_2$ ($ml.kg^{-1}.min^{-1}$) values for asthmatic subjects following the 1 x 30s, 2 x 15s, 3 x 10s tests were 41.45, 42.37 and 44.39 $ml.kg^{-1}.min^{-1}$, respectively. The non-asthmatic mean $\dot{V}O_2$ ($ml.kg^{-1}.min^{-1}$) values were 37.89, 42.57 and 43.07 $ml.kg^{-1}.min^{-1}$, respectively. There were no significant differences reported in the peak heart rates between asthmatic and non-asthmatic subjects ($P<0.16$) (Table 6.3). Significant differences however were reported in the $\dot{V}E$ ($l.min^{-1}$) and RER between asthmatics and non-asthmatics ($P<0.01$, and $P<0.00$), respectively. The mean $\dot{V}E$ ($l.min^{-1}$) for the asthmatic subjects for the three tests 77.25, 77.61 and 80.53, respectively. The non-asthmatic subjects displayed significantly higher mean $\dot{V}E$ ($l.min^{-1}$) for the three high intensity tests, these were 86.63, 92.70 and 97.51 $l.min^{-1}$, respectively.

Repeated measures analysis revealed significant interaction occurred between asthmatics and non-asthmatics for plasma lactate ($P<0.00$). The asthmatic subjects displayed lower lactate concentrations ($mmol.l^{-1}$) compared with the non-asthmatics following the 1 x 30s and 2 x 15s high intensity tests (Figures 6.8 and 6.9). There was non significant difference between asthmatic and non-asthmatic subjects in the plasma lactate levels following the three the 3 x 10s test (Figure 6.10). The plasma adrenaline responses following the three tests displayed significant differences between asthmatic and non-asthmatic subjects ($P<0.02$). Newman-Keuls post hoc analysis identified where the significant differences were

present among group means. The non-asthmatic subjects displayed higher adrenaline levels in all three tests compared with that of the asthmatics (Figure 6.11). The 1 x 30 s high intensity test demonstrated the greatest adrenaline responses compared with the 2 x 15 s and 3 x 10 s test in the non-asthmatic and asthmatic subjects. The 1 minute post plasma adrenaline values for the three tests (1 x 30 s, 2 x 15s and 3 x 10 s) for the asthmatic subjects were 1.55, 1.05 and 1.19 ($nmol^{-1}$), respectively. The non-asthmatic 1 minute post plasma adrenaline values were 3.89, 2.72 and 2.24 ($nmol^{-1}$), respectively. The nor-adrenaline values showed similar values between the three high intensity tests (Figure 6.12). There were no significant differences in the plasma nor-adrenaline levels ($nmol^{-1}$) between asthmatic and non-asthmatic subjects.

The measurements of pH, HCO_3 and hemoglobin did not display any significant differences between asthmatic and non-asthmatics in any of the variables (Appendix E3.3 & E3.4). Figures 6.13, 6.14 and 6.15 present the responses in these variables collapsed for both asthmatic and non-asthmatic subjects over the three protocols. Similarly no significant differences were reported among the results from the three tests, however differences were found over time with pH, HCO_3 and hemoglobin being significantly different in rest than in recovery responses (Table 6.4). The resting pH levels range from 7.35 to 7.38, whereas the mean Nadir pH levels ranged from 7.17 to 7.24 for the asthmatic and non-asthmatic subjects. The recovery pH displayed significant reduction within the first minute of recovery and these values were sustained over the remaining 12 minute period (Figure 6.13). The HCO_3 values displayed a significant difference between pre and post values of the high intensity test (Figure 6.14). These pre values ranged from 24.60 to 27.62 (mmol/L) and the mean post values from 14.48 to 21.30 (mmol/L). Once again there was no significant difference in the HCO_3 values obtained in the post recovery values. Hemoglobin displayed a significant difference between the pre values and the mean post hemoglobin responses following the three high intensity tests (Figure 6.15). The recovery hemoglobin values demonstrated a significant increase when compared to the pre values and plateaud for the remaining 12 minutes.

Table 6.0 Descriptive characteristics of Subjects

	CONDITIONS			
	Asthmatics		Non -asthmatics	
Variable	Mean	SEM	Mean	SEM
Age (yr)	15.04	(0.26)	14.53	(0.21)
Mass (kg)	58.08	(3.80)	61.78	(3.10)
Height (cm)	166.4	(2.4)	168.5	(1.5)
BMI (kg/m^2)	20.79	(0.94)	20.94	(0.74)
Tanner (1-5)	4.0	(0.2)	4.0	(0.3)
Skinfolds (mm) (Sum of Six)	63.11	(4.39)	65.82	(2.89)
Salivary Testosterone ($pmol.l^{-1}$)	179.6	(17.3)	184.2	(11.34)

(M±SEM)

Figure 6.1

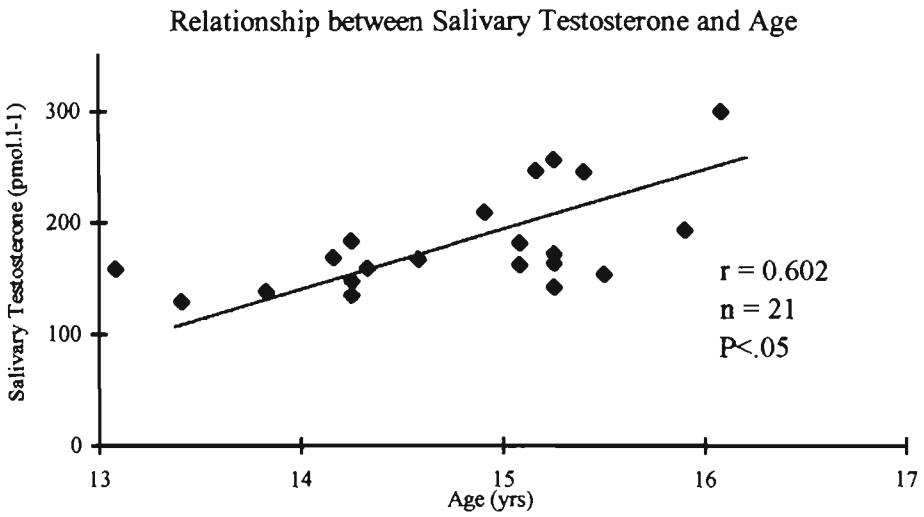


Figure 6.2

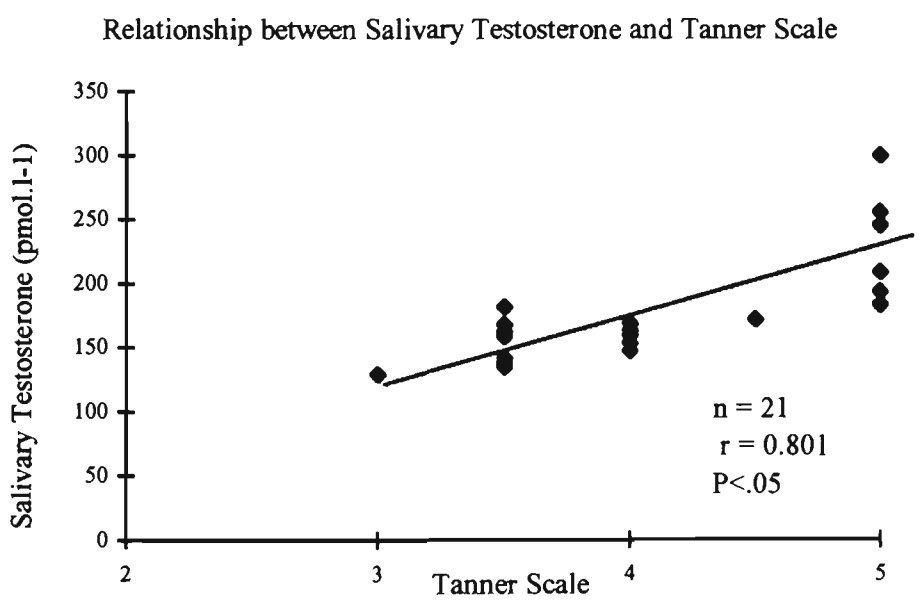


Table 6.1 Maximal effort profile for the peak $\dot{V}O_2$ test

Variable	Asthmatics		Non-asthmatics
$\dot{V}O_2$ ($ml.kg^{-1}.min^{-1}$)	54.57		51.85
	(2.00)		(1.56)
Mean V_E ($l.min^{-1}$)	90.71		92.34
(last 6min)	(3.63)		(5.78)
Peak V_E ($l.min^{-1}$)	118.26		125.92
	(5.95)		(8.33)
Heart rate (bpm)	197.2		201.3
	(1.5)		(2.4)
Respiratory exchange ratio	1.12	*	1.19
	(0.01)		(0.01)
Peak % reduction in FEV_1	25.87	*	1.25
	(4.74)		(0.82)
Predicted MVV	119.04		128.40
	(5.67)		(5.44)

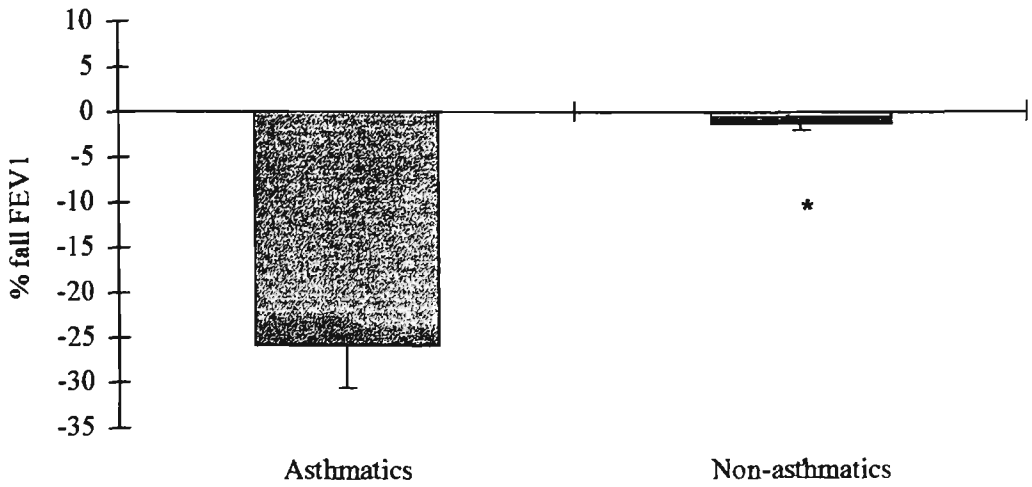
M±SEM

A = Asthmatics

N =Non asthmatics

* denotes significant differences between conditions $P<0.05$

Figure 6.3 Maximal percentage fall in FEV_1 following peak V O_2 test



*denotes significant difference P<0.05

Figure 6.4 Ventilation (l min^{-1}) measurements during the peak V O_2 test

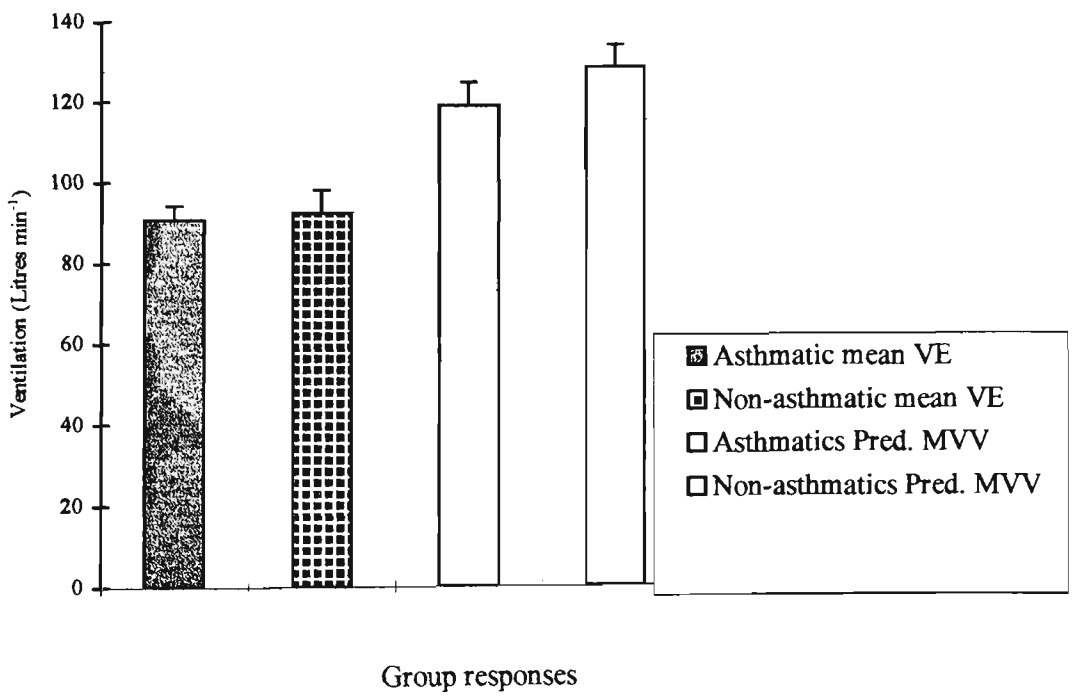


Table 6.2 **Anaerobic performance characteristics from the high intensity exercise test**

Condition	A	NA	A	NA	A	NA
Protocol	1 x30		2 x15		3 x10	
Variable						
Peak power(w)	567.3	589.9	569.8	592.7	559.4	587.1
	(41.5)	(32.7)	(40.4)	(33.0)	(41.7)	(33.6)
Mean power(w)	478.0	497.3	465.2	462.2	444.5	457.9
	(30.5)	(27.9)	(30.0)	(34.1)	(30.2)	(31.0)
Relative peak power ($w_{\bullet}kg^{-1}$)	9.7	9.8	9.8	9.9	9.6	9.8
	(0.2)	(0.3)	(0.4)	(0.2)	(0.3)	(0.2)
Relative mean power ($w_{\bullet}kg^{-1}$)	8.2	8.3	7.9	7.7	7.7	7.67
	(0.3)	(0.3)	(0.7)	(0.4)	(0.3)	(0.3)

M±SEM

A = Asthmatics

N =Non asthmatics

Table 6.3 Mean and peak physiological responses from the high intensity exercise test

Condition	A		NA	A		NA	A		NA
Protocol	1 x30			2 x15			3 x10		
Variable									
Mean $\dot{V}O_2$ ($ml.kg^{-1}.min^{-1}$)	41.45 (1.11)		37.89 (1.40)	42.37 (1.35)		42.57 (2.46)	44.39 (1.56)		43.07 (1.51)
Mean V_E ($l.min^{-1}$)	77.25 (3.34)	*	86.63 (4.99)	77.61 (4.13)	*	92.7 (6.57)	80.53 (3.81)	*	97.51 (3.69)
Heart rate (bpm)	180 (2)		182 (2)	174 (2)		181 (2)	178 (2)		182 (2)
RER	1.28 (0.02)	*	1.32 (0.03)	1.27 (0.02)	*	1.31 (0.02)	1.22 (0.01)	*	1.32 (0.01)

M±SEM

A = Asthmatics

N =Non asthmatics

*denotes significant difference between asthmatic and non-asthmatic subjects within a specific protocol.

Figure 6.5 Percentage change in FEV_1 in asthmatic subjects following high intensity exercise tests

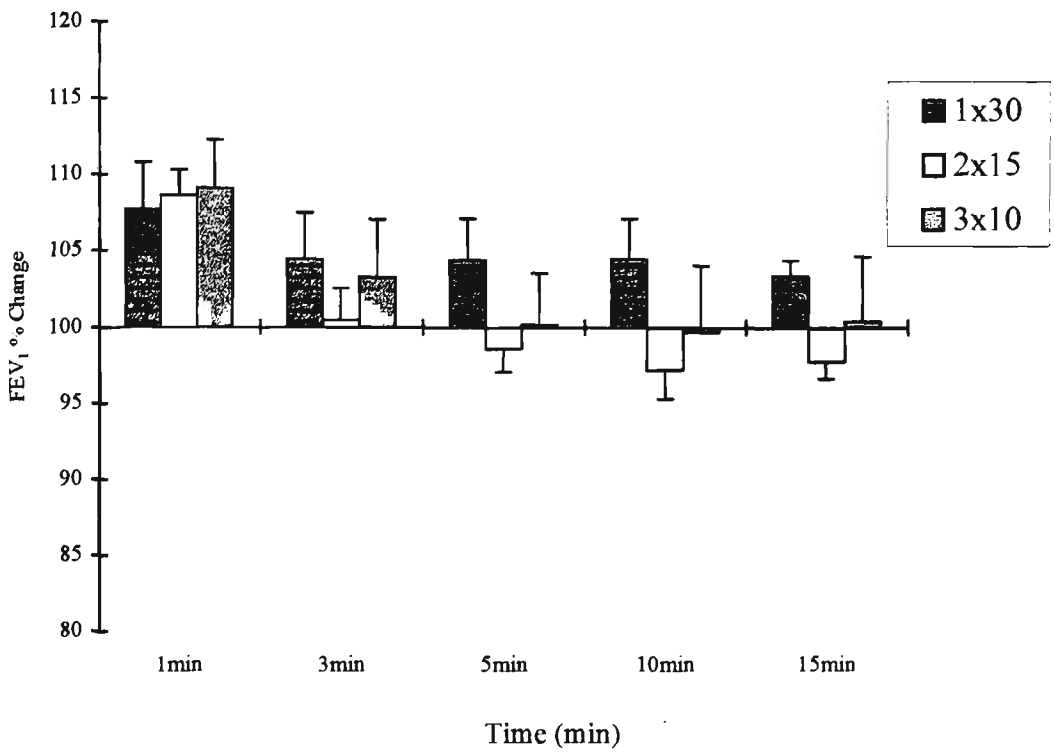


Figure 6.6 Percentage change in FEV_1 in Non-asthmatic subjects following high intensity exercise tests

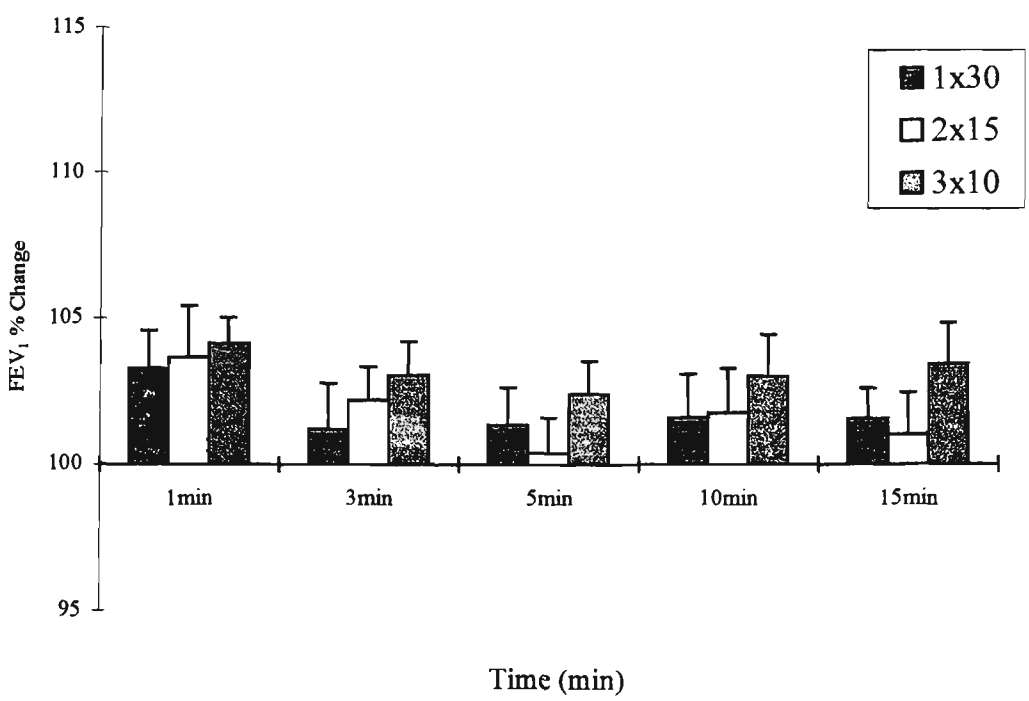


Figure 6.7 Peak reduction in $FEF_{25-75\%}$ of asthmatic subjects following high intensity tests

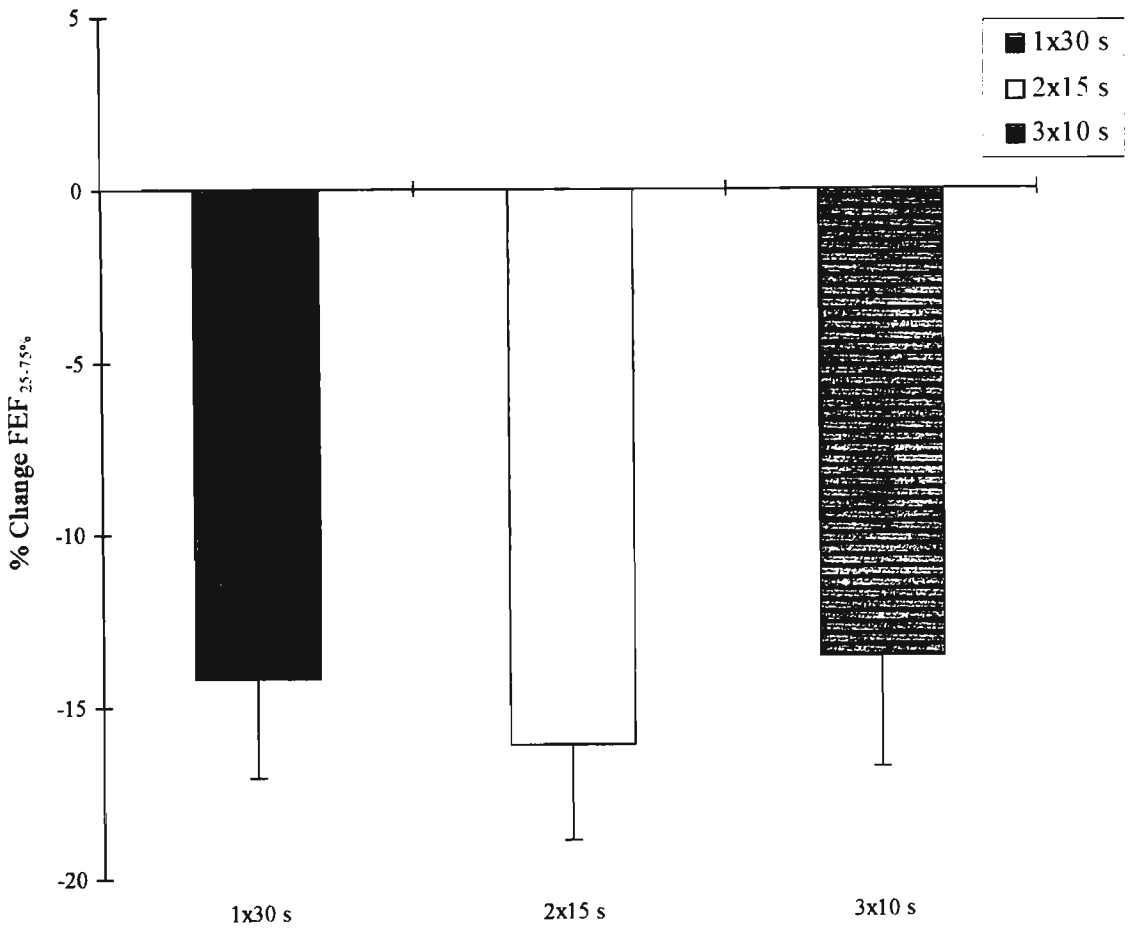
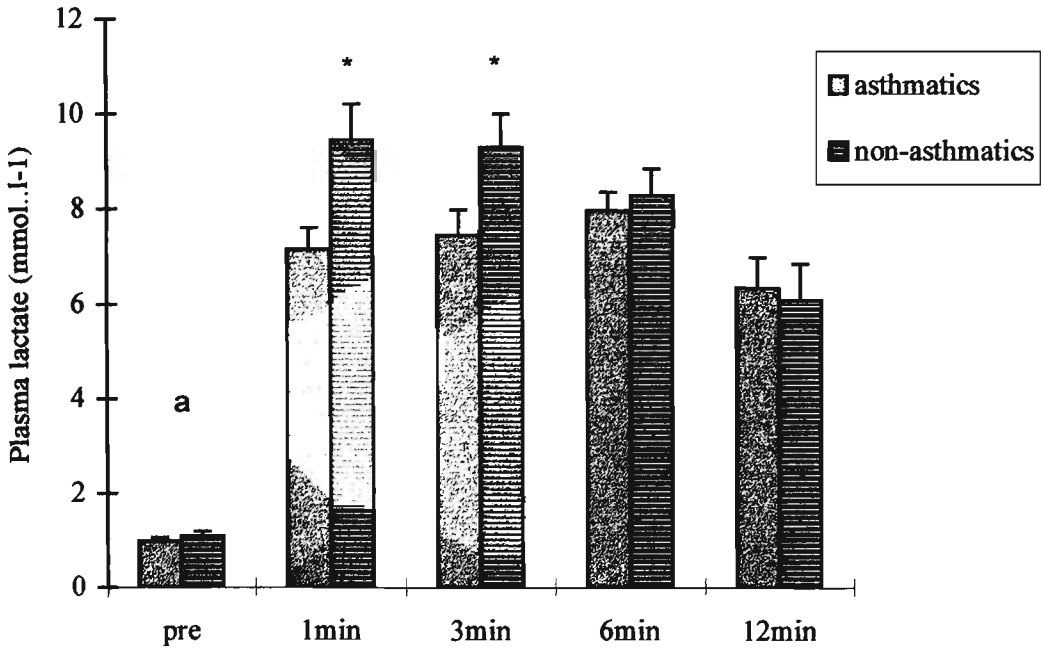


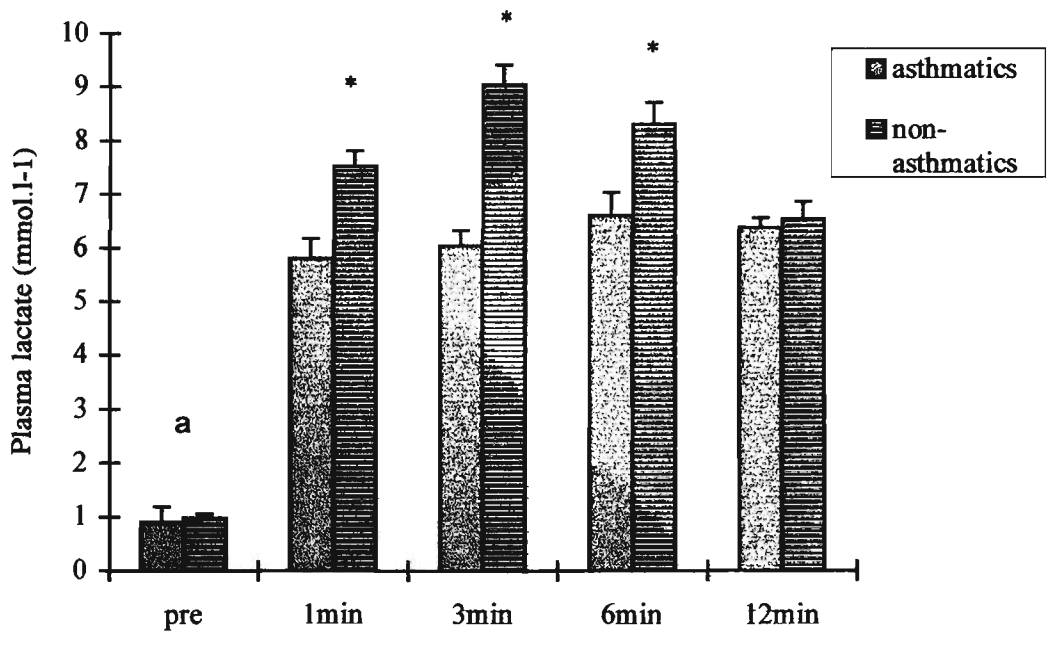
Figure 6.8 Plasma lactate concentrations (mmol.l^{-1}) prior to and following 1 x 30 s test



*denotes significant difference between asthmatic and non-asthmatic subjects P<0.05

a denotes significant difference between rest and post values P<0.05

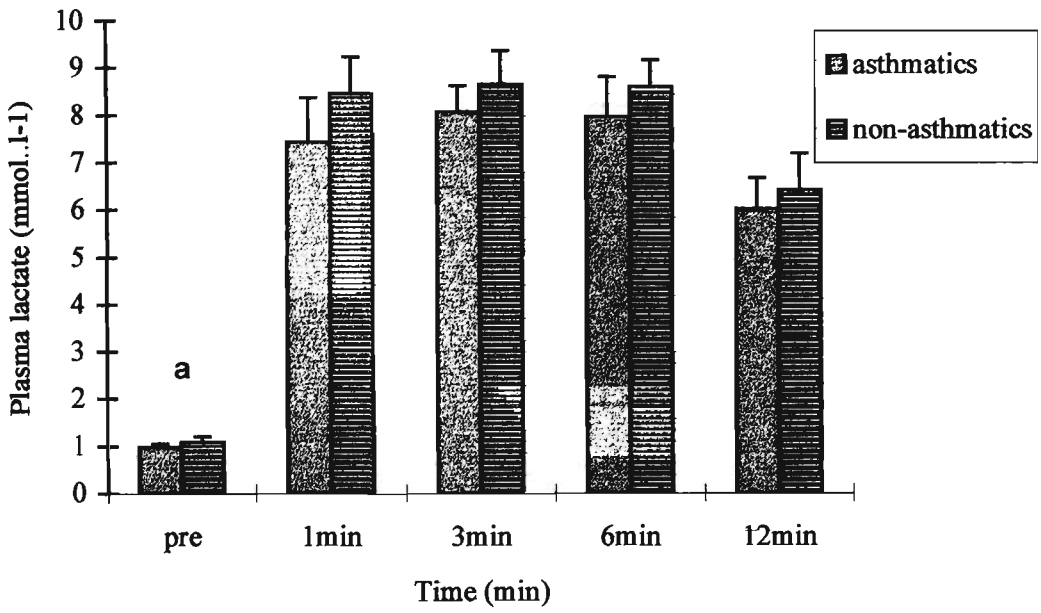
Figure 6.9 Plasma lactate concentrations (mmol.l^{-1}) prior to and following 2 x 15 s test



*denotes significant difference between asthmatic and non-asthmatic subjects P<0.05

a denotes significant difference between rest and post values P<0.05

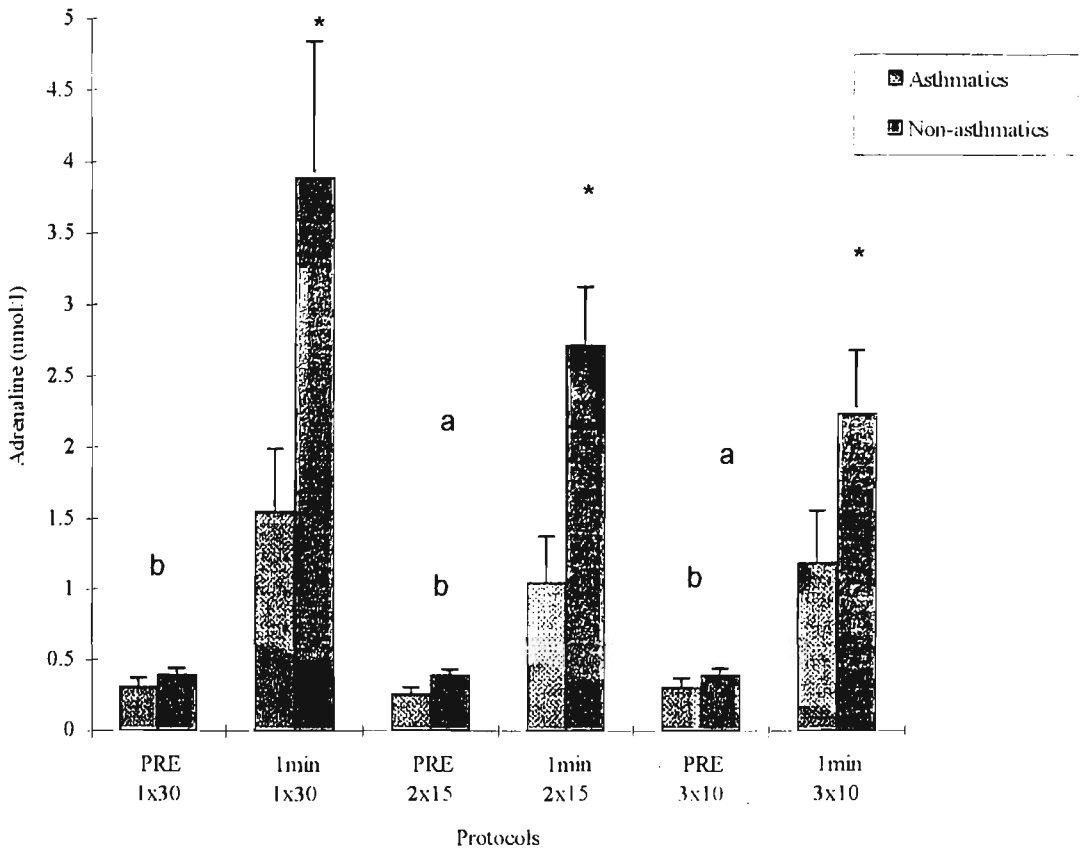
Figure 6.10 Plasma lactate concentrations (mmol.l^{-1}) prior to and following 3 x 10 s test



Pre exercise and Recovery time intervals

*denotes significant difference between rest and post values $P<0.05$

Figure 6.11 Plasma Adrenaline responses from the three high intensity protocols

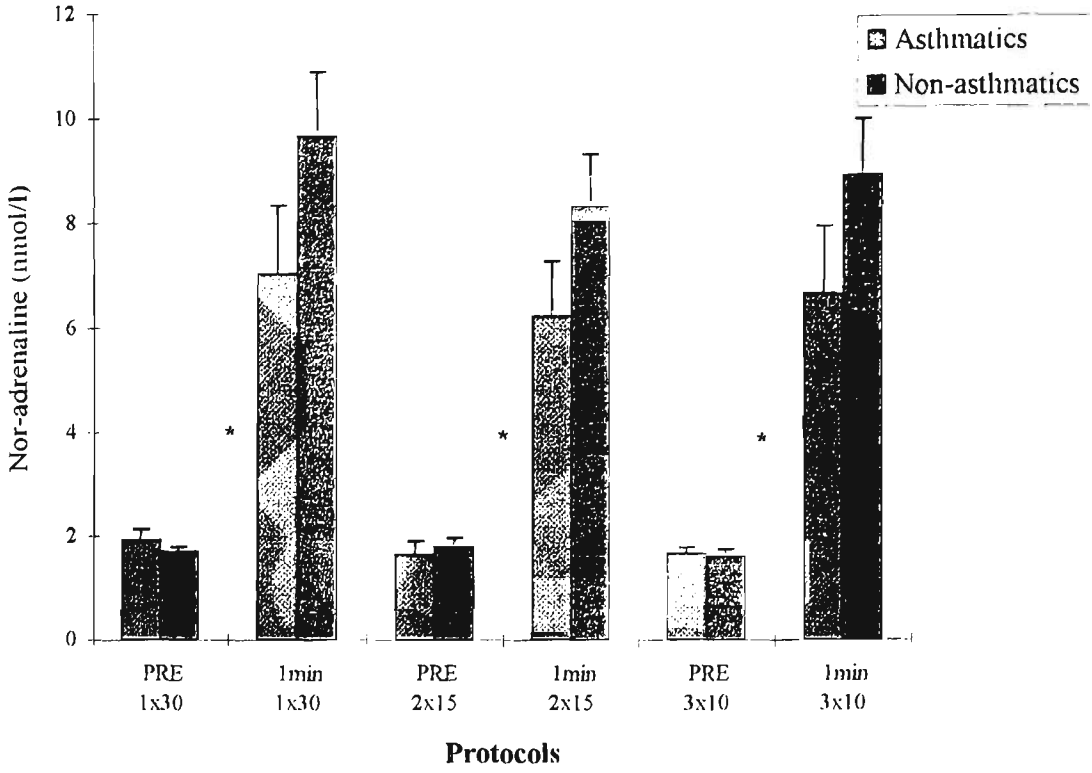


*denotes significant difference between asthmatics and non-asthmatics P<0.05

a denotes significant difference between 1 x30s and the 2 x 15s and 3 x10s exercise test P<0.05

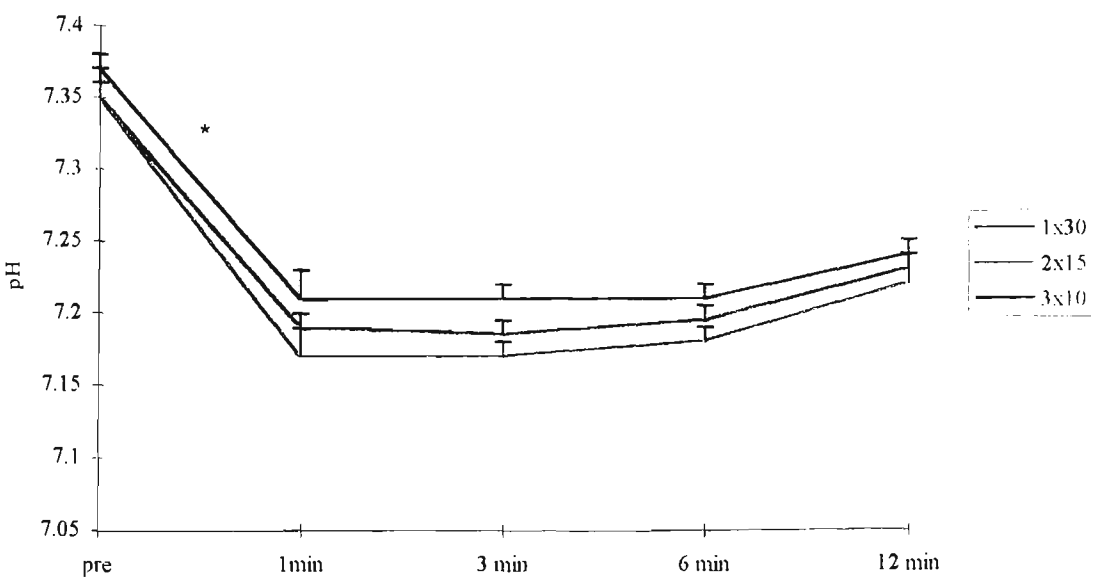
b denotes significant difference between pre and post responses P<0.05

Figure 6.12 Plasma Nor-adrenaline responses from the three protocols



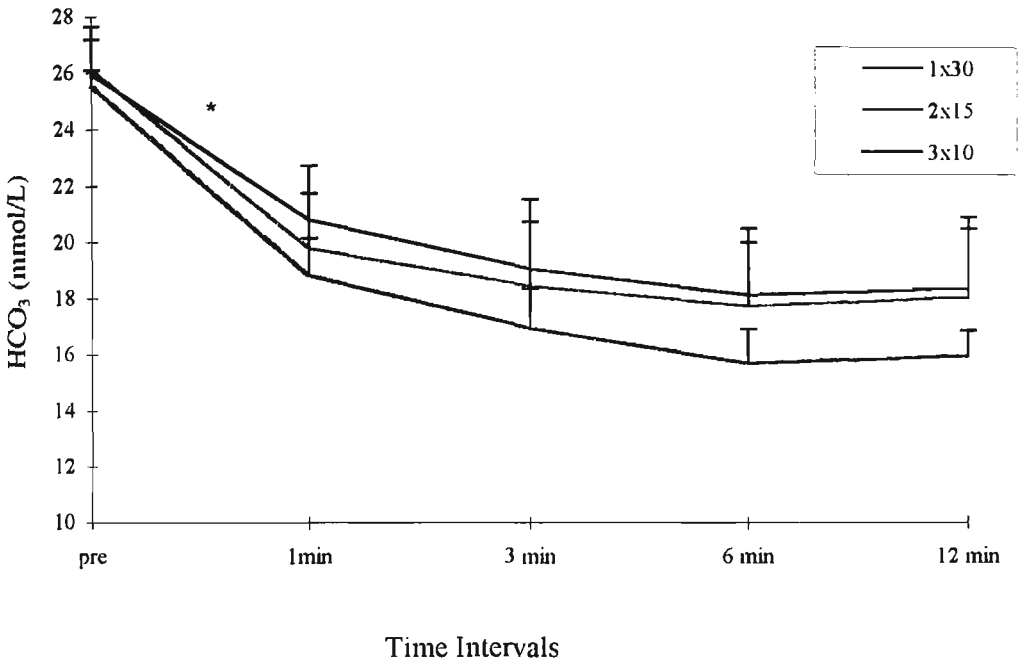
*denotes significant difference between pre and post responses P<0.05

Figure 6.13 pH responses from pre and post high intensity protocols



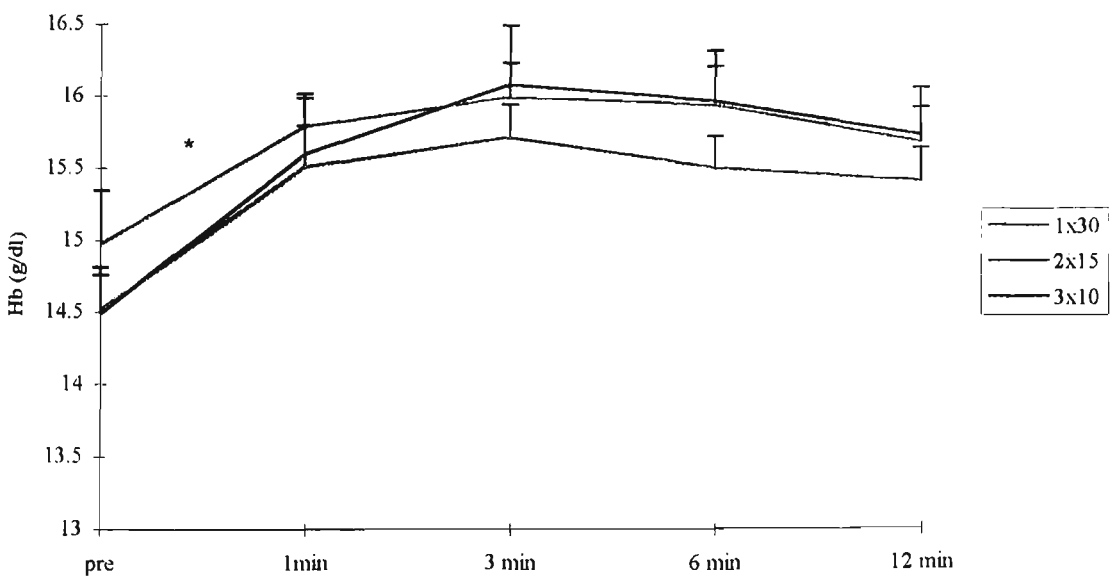
*denotes significant difference between pre and post time intervals P<0.05

Figure 6.14 HCO_3 responses from pre and post high intensity protocols



*denotes significant difference between pre and post time intervals $P<0.05$

Figure 6.15 Hb responses from pre and post high intensity protocols



Discussion

FEV_1 values are reported to be an acceptable index of ventilation in the large airways, whereas $FEF_{25-75\%}$ values are more indicative of small airway conductance (McFadden et al., 1974). The FEV_1 responses were not significantly different across the three high intensity tests and between the asthmatic and non-asthmatic subjects. Therefore the results from the present study indicated no reduction in FEV_1 responses following the high intensity tests. More specific measurements of ventilation in the small airways denoted by values for $FEF_{25-75\%}$ (also known as the MMEF) indicated a significant reduction airway in asthmatic when compared to non-asthmatic subjects (Figure 6.7). The $FEF_{25-75\%}$ responses had a significant reduction following all high intensity tests and no differences were reported between the testing protocols. The findings from the present study are in agreement with Inbar et al. (1981), who demonstrated that short exhaustive exercise for the duration of 40-50s resulting in a significant reduction in mid-maximal expiratory flow (MMEF) and without significant fall in FEV_1 values. The lack of difference in a reduction in FEV_1 responses between asthmatics and non-asthmatics has also been previously documented in asthmatics during exercise periods of less than 2 minutes, however, the workloads were not involving supramaximal intensities performed intermittently (Anderson et al., 1971, Jones et al., 1962, Silverman et al., 1972). Thus, it appears that a reduction in smaller rather than larger airway functions may result from high intensity intermittent exercise.

An important aim of this investigation was to investigate the asthmatics anaerobic performance characteristics compared to non asthmatics. Anaerobic performances were extremely similar between the two groups in this study (Table 6.2). The mean power and peak power (watts) from the study displayed similar values compared to the work of Inbar and Bar-Or (1986) and Bar-Or (1983). From the present study the two groups were well matched with strong homogeneity in their descriptive characteristics, salivary testosterone and maximal effort data. It was crucial to assess maturational status as it has been well documented that anaerobic performances of children compared with adults are significantly inferior and that anaerobic metabolism changes during growth (Bar-Or, 1983, Eriksson et al., 1972, Sargeant, 1989). Falgairette et al. (1991) demonstrated that changes in anaerobic metabolism are strongly related to growth and sexual maturation in young males. To spite the large number of studies published which have examined asthmatic children, performance characteristics have been only expressed in relation to chronological age rather than maturational development. From studies which have investigated exercise performances, physiological responses and sympathoadrenal activity of asthmatic children, it is likely that many of these responses may have been influenced by the strong intervening variable of maturational status, even though in some studies chronological age was well matched in control subjects (Amirav et al., 1994, Karila et al., 1992, Morton et al., 1982, Schnall and Landau, 1980). This was supported in the present study by the salivary testosterone levels producing a higher correlation with maturational status denoted by the

Tanner scale than when salivary testosterone was correlated with chronological age. Both however, confirmed positive relationships (Figure 6.1 and 6.2). With the close relationship between the asthmatics and non-asthmatics mean salivary testosterone levels strengthens the homogeneity and subsequently decreases intra variability.

One of the major findings from this study which contributes to the controversy surrounding the asthmatic subjects' sympatho-adrenal response was the blunted adrenaline responses with the asthmatic subjects compared with the non-asthmatic subjects following the three high intensity tests (Figure 6.8). Various studies have investigated sympathoadrenal activity during exercise and have shown no differences in catecholamine responses between asthmatic and non-asthmatic subjects (Amirav et al., 1994, Berkin et al., 1988, Chryssanthopoulos et al., 1978, Hulks et al., 1991, Larsson et al., 1982, Zielinski et al., 1980). Conversely, other studies have demonstrated asthmatic subjects with attenuated levels of adrenaline during exercise (Barnes et al., 1981, Reinhardt et al., 1980, Van Aalderen et al., 1992, Warren et al., 1982). These conflicting findings may be partially related to the limitations with subject selection, different methods for assay analyses (radioenzymatic and HPLC), varying durations of withholding β_2-agonists, and the exercise protocol (intensity and duration).

While the level of plasma adrenaline during exercise is reported to be sufficient to cause bronchodilation, the presence of a β-adrenoceptor blockade may cause bronchoconstriction (McNeil, 1964, Warren and Dalton, 1983). It was evident from the FEV_1 responses in the present study that there may have been an initial dilation response from the asthmatic subjects following the high intensity tests (Figure 6.5), even though they displayed a lower adrenaline level compared to the non-asthmatics (Figure 6.8). A study conducted by Pichurko et al. (1986) on 10 asthmatics (mean age 23 years) required them to perform repetitive exercise bouts (4 min) on a cycle ergometer. They found that there was an increase in endogenous sympathoadrenal responses which they postulated influenced the severity of asthma.

In the present study the adrenaline levels from the asthmatics were blunted compared with the non-asthmatics but the nor-adrenaline responses showed no significant difference between the two groups (Figures 6.8 and 6.9). It has been shown that β_2 receptors are controlled by circulating adrenaline whereas β_1 receptors are regulated by nor-adrenaline (Barnes 1986). In previous studies it has been suggested that exaggerated nor-adrenaline levels may cause bronchoconstriction via α-adrenoceptors. Without a rise in adrenaline levels, it may stimulate the α-adrenoceptors on mast cells to produce an increase in the mediator release (Beil et al., 1977, Kaliner et al., 1972, Reinhardt et al., 1980). It is unlikely however, that this response occurred in the present study because the marked vasoconstriction would have resulted in a significant reduction in the FEV_1 responses of the asthmatics subjects following high intensity exercise (Figure 6.7). This response was not observed in any of the high intensity tests.

The asthmatic subjects' mean VE (l. min^{-1}) during the high intensity tests exceeded 60% of their predicted MVV for a period of 1 minute which incorporated only 30s of total work (Table 6.3). Therefore the critical ventilatory threshold was not maintained for long enough to provoke EIA. The results of the present study are therefore unable to contribute to the uncertainty surrounding the precise mechanisms for EIA provocation, whether it was initiated via evaporative water loss causing a transient in osmolarity or a rapid rewarming of the airways by reactive hyperaemia of the bronchial circulation (Anderson, 1984, McFadden 1990). Greater understanding may be available from future research extending the total work time to 60 seconds.

It is difficult to ascertain why the asthmatics had demonstrated an attenuated adrenaline response significantly lower plasma lactate levels, and produced a similar work output when compared to the non-asthmatics. Lehmann et al. (1981) reported that there was an identical increase in lactate and catecholamine levels following high intensity exercise. In the present study there were also similar increases in lactate and adrenaline responses in both groups. It does not explain however, why these lower responses occurred in the asthmatic when compared to non-asthmatic subjects. An interesting study performed by Hochachka et al. (1982) on high altitude animals found that these animals had an upward scaling of oxidative capacity (indicated by absolute activities of citrate synthase (CS) and hydroxyaclCoA dehdrogenase HOAD) and a downward scaling of anaerobic/aerobic metabolic potentials of the heart (indicated by low ratios of lactate dehydrogenase (LDH)/CS and LDH/HOAD). The authors also reported high ratios of pyruvate kinase/LDH). From their findings they suggested that animals exposed to long term adaptation to high altitude had an increased rate at which oxygen and substrates can be fluxed through the system. This theory of "enhanced flux capacity" was supported by increased enzyme activities and mitochondrial abundance. Is it then possible that the asthmatics in the present study have developed similar adaptations to the high altitude animals and subsequently adopted responses more sensitive to hypoxic conditions than non-asthmatics and moved more rapidly into an aerobic preference for energy demand? Related to this postulation may be studies reporting that hypoxia reduces arterial oxygen partial pressure and represents an additional stress to the ventilatory, circulatory, and metabolic processes during exercise. Hypoxia reduces both $\dot{V}O_2$ max and anaerobic threshold even in the presence of a catecholamine-induced tachycardia (Cooper et al., 1986, Favier et al., 1985, Springer et al., 1991). The theory therefore postulates that if asthmatics are more sensitive to hypoxic conditions, the aformentioned adaptations may account for the attenuated levels of plasma lactate and adrenaline in asthmatic subjects when compared to non-asthmatic subjects. The implication of this theory is that asthmatics have frequent hypoxemia. This however, seems unlikely. Alternate explanations are difficult to establish.

The intensity of exercise performed by subjects in this study was supramaximal. This means it was predominantly anaerobic in nature and likely to have induced metabolic acidosis. Among other triggers the chemo and mechanoreceptors are predicted to have increased the ventilatory drive under

these high intensity exercise conditions. Dempsey (1984), demonstrated that when healthy subjects performed heavy short-term exercise, it promoted hyperventilation which was accompanied by increased metabolic acid production. This finding may be associated to the finding in the present study that the non-asthmatics displayed high RER values, higher VE values and lower pH values (Table 6.3 and 6.4) when compared to their asthmatic counterparts. The underlying mechanisms remain difficult to explain. The previous analogy made on asthmatics with high altitude animals may also be associated with the lower levels of plasma lactate, RER and VE of the asthmatic subjects when compared to non-asthmatic subjects.

It is also postulated that the prolonged treatment of asthma with β_2 agonists may reduce the sensitivity of the β_2 adrenoreceptors and subsequently reflect differences in the susceptibility of different β_2 adrenoreceptors to desensitization (Gibson et al. 1978). Martinsson et al. (1985) examined β_2 adrenoceptor responsiveness both in vivo and in vitro in subjects with EIA, subjects with asthma which was not EIA, and control subjects. Their findings demonstrated that the β_2 -adrenoceptor mediated responses were reduced both in vivo and in vitro in EIA subjects, but not in the asthmatic patients without EIA. From their data they concluded that β_2-adrenoceptor responsiveness was reduced only in EIA subjects. It has been previously reported that seven to eight days is required for normalisation of β_2 -adrenoceptor sensitivity in the lungs of subjects who are currently being treated with β_2 -agonists (Holgate et al., 1977). It is possible in the present study that the asthmatic subjects were requested to withhold medication for a minimum of 8 hours may have only slightly influenced the plasma adrenaline responses by meeting these pre-testing demands.

Sympathoadrenergic responses to supramaximal exercise have been found to increase after anaerobic training (Okhuwa et al., 1984).The attenuated levels of adrenaline responses in asthmatic subjects following exercise may have therapeutic implications in the treatment of EIA (Barnes et al., 1986). More specifically, implementing anaerobic training regimes for EIA patients or athletes may enhance their sympathoadrenal response and subsequently provide a greater than normal defence against bronchoconstrictor influences. It was clearly evident that supramaximal exercise of less than one minute duration had no effect on bronchoconstrictor stimuli. This finding provides positive support for the benefits that may be gained by asthmatic populations from participating in this type of activity.

Chapter Seven

Summary and Recommendations

Summary and Recommendations

The following chapter involves summaries and recommendations from each study performed in this thesis. It presents major findings and specific recommendations emanating from these findings. It also provides general recommendations and a conclusion to the series of three investigations conducted for this thesis.

Summary and Recommendations for Study One

In study one, a group of preadolescent males with asthma performed a series of high intensity supramaximal exercises to exhaustion. The high intensity tests represented 110 and 130% of maximal effort which was predicted from a linear regression equation constructed from data of both the peak oxygen uptake test and the individual submaximal VO_2 /running speed responses. The AOD values were compared with a carefully matched group of young subjects without asthma. Preventative medication was administered to the asthmatic subjects prior to all testing. The results in the performances of the two groups indicated no significant differences in the measures of anaerobic metabolism and respiratory responses.

Table 7.0 presents a summary of the findings and the recommendations of the first research investigation in this thesis. The major focus of Study One was to ascertain whether a group of children identified as being asthmatics had inferior anaerobic characteristics compared with non-asthmatic children. The asthmatics all tested positively to a hyperosmolar saline provocation test. These results supported the hyperosmolar saline provocation test as an appropriate diagnostic tool for the detection of asthma. Therefore recommendation one from this study is to continue the use of this test for future testing as a diagnostic assessment for asthma and the possible assessment of EIA.

Table 7.0 Summary of major findings and recommendations from Study One

Summary of Major Findings	Recommendations
1. Asthmatic subjects were tested positively to a hypersaline provocation test.	1. Continued use of hypersaline provocation test as an appropriate diagnostic tool for the presence of asthma.
2. No differences were found between asthmatic and non-asthmatic children in both relative and absolute peak $\dot{V}O_2$ ($ml.kg^{-1}.min^{-1}$ and $l.min^{-1}$)	2. Future studies continue to pursue homogeneity of sample populations.
3. Asthmatics displayed no difference in their anaerobic characteristics compared to the non-asthmatic subjects which were measured by the AOD method.	3. Further research should be conducted to determine the results of the supramaximal runs by investigations into the following areas; the reliability of the AOD method with or without medication, variety of environmental differences on the AOD method and examination of blood borne indices.
4. No bronchoconstriction occurred in either group under either of the test intensity conditions.	4. Future research should be extended to determine the respiratory responses from supramaximal runs without medication.

The subjects in study one were largely homogeneous in their physical characteristics and maximal effort profile. This was reflected in both their relative and absolute peak $\dot{V}O_2$ and anthropometric measurements. Chapter two in this thesis highlights the difficulties inherent in interpreting results from largely non-homogenous populations. Therefore, it is crucial that future studies strive for homogeneity in this area with particular emphasis to fitness, age, different severity of asthma and matching maturational status between young populations with and without EIA.

Recommendation three from the first study calls for further understanding of the accumulated oxygen deficit (AOD) responses in young populations with EIA. This method had been previously examined in young populations (Carlson and Naughton, 1993, Medbø et al. 1988) and is a non-invasive measure of anaerobic performance which appears to be sensitive enough to detect anaerobic differences between populations of children and adults. In Study One no differences were found in the AOD values of the

asthmatics compared with the non-asthmatic subjects. Further anaerobic testing therefore may provide a broader understanding of high intensity exercise responses in populations with EIA. This research could include investigations of the sympathoadrenal responses during the AOD method. Because the method has been validated with non-asthmatic populations it may warrant further modifications for different asthmatic populations. Further investigations with these populations should take place to determine the reliability of the AOD method with and without medication. These experiments could also extend into protocols using different types of medication used for the treatment and prevention of EIA. It could also be questioned whether a variety of environmental differences have an effect on the results of the AOD method. For example, manipulations of relative humidity may significantly influence the exercise responses of the EIA subject.

The asthmatic subjects displayed no bronchoconstriction and no differences in their respiratory responses following the supramaximal runs compared with the non-asthmatic subjects. Therefore the final recommendation from this study is that future research investigates the respiratory responses of asthmatic subjects without medication prior to supramaximal exercise tests.

Summary and Recommendations for Study Two

Study Two examined the effects of repetitive high intensity work on asthmatic children. The major findings from this study are presented in Table 7.1. In this study various intermittent exercises performed for a total duration of 6 minutes produced a similar stimulus for EIA as the stimulus provoked from continuous exercise (Figure 5.7). Previous studies have demonstrated that asthmatic subjects produced less bronchoconstriction and in some cases a bronchodilatory response (de Bisschop et al. 1992, Schnall and Landau, 1980) following intermittent exercise. One of the possible explanations for the differences in the present findings and the previous research may be found in the design of a protocol which imposed equal ventilatory responses among the exercise bouts for the young asthmatic and non-asthmatic subjects.

Table 7.1 Summary of major findings and recommendations from Study Two

Summary of Major Findings	Recommendations
1. The asthmatics were diagnosed as having EIA from a peak VO_2 test.	**1.** The modified $\dot{V}O_2$ protocol should be continued as an effective diagnosis of EIA.
2. Asthmatic and non-asthmatic subjects performed four treadmill exercise tests designed to produce equal amounts of work and elicit a ventilatory response greater than 60% of predicted MVV.	**2.** Examine blood borne indices of exercise metabolism following the exercise protocols. Expand present protocol using different intensities, durations and work rest ratios.
3. The four exercise tests displayed no significant differences between respective values for asthmatics and non-asthmatics for HR (175 and 182 bmp), VE (39.6 - 46.0 $L.min^{-1}$) and VO_2 (37.3 - 40.9 $ml.kg^{-1} min^{-1}$).	**3.** Broaden the understanding of the exercise responses to this protocol by incorporating a range of populations.
4. The percent fall index in FEV_1 over the four tests ranged between 20 and 34% for asthmatics and between -0.37 and -0.63 for the non-asthmatics.	**4.** Examine the respiratory responses (FEV_1 and $FEF_{25-75\%}$) during the intermittent exercise protocols.

In Study Two the diagnosis of EIA was effectively obtained through a modified peak VO_2 test. The focus of the first recommendation from this study therefore, is to continue and further develop the use of a modified peak VO_2 test as an effective and specific test for the diagnosis of EIA. The specificity of the nature of this test simulates closely with the stresses likely to be imposed in the physical activity encountered in everyday life of the young asthmatic.

Recommendation two from this study calls for the extension of investigations incorporating blood borne indices of exercise metabolism. The high intensity intermittent exercise tests used in Study Two were designed to utilise anaerobic pathways and concomitantly stimulate sympathoadrenal responses (Lehmann et al., 1981). An obvious extension of the existing protocol would be to investigate the blood borne indices which may reflect the sympathoadrenal responses such as adrenaline and nor-adrenaline following the high intensity exercise bouts. Blood borne indices of the sympathoadrenal responses could also be examined under different high intensity exercise stresses. Alternative exercise stresses could be designed using various intensities, durations, and work to rest ratios within the protocol. Some potentially prescriptive information could be obtained from protocols specifically replicating the work to rest ratios observed in popular intermittent-based sporting activities.

Recommendation three refers to an extension of the research into studies focusing on greater homogeneity among the targeted populations with EIA. There is some suggestion in the literature that maturational status of subjects can influence the anaerobic responses of pubertal-aged subjects. Therefore longitudinal studies profiling the anaerobic and sympathoadrenal responses through the stages of puberty may again provide useful insight into the responses to high intensity exercise among pubertal populations with EIA. Additional research could also address the need for homogeneity in the selection of subjects with similar degrees of asthma. Recent research has further indicated that homogeneity may be warranted among the activity levels of populations with EIA even within the same age group, maturational status, or degree of asthma.

Intermittent exercise protocols performed by asthmatic populations have previously resulted in a bronchodilatory response. This response was postulated as a defense mechanism against a bronchoconstrictor influence imposed by catecholamines (Pichurko et al., 1978, Schnall and Landau, 1980). In Study Two however, there was no evidence to suggest that during intermittent tests the asthmatic subjects demonstrated a bronchodilatory response in post exercise measurements. The percent fall index in FEV_1 over the four tests among asthmatic subjects ranged between 20 and 34%. Similar exercise stresses elicited respiratory responses without any fall in FEV_1 for the non-asthmatic subjects. Because of the different results appearing within the literature, recommendation four suggests that there is a strong need to examine the respiratory responses throughout intermittent exercise protocols. This would provide an increased understanding of respiratory responses during the exercise and may also indicate how closely these responses are reflected in the data being collected for the blood borne indices of exercise metabolism in subjects with EIA.

Summary and Recommendations for Study Three

Table 7.2 presents the summary and recommendations from Study Three. Study Three examined the physiological responses following a number of high intensity exercise bouts involving a duration of less than one minute. The young asthmatic subjects' responses were compared with non-asthmatics. The three exercise tests did not have any bronchoconstricting influence on the large airways which would have been identified as a significant reduction in FEV_1 responses (Figures 6.5 and 6.6). There was however, a significant fall in $FEF_{25-75\%}$ values which was indicative of obstruction of the small airways (Figure 6.7). There were no significant differences in anaerobic performances as measured by power output between the two groups (Table 6.2). The major finding in this study was a reduced adrenaline response following the three high intensity tests in the asthmatic subjects when compared to non-asthmatic subjects. The respective mean adrenaline values for the three exercise protocols in the asthmatic subjects were 1.55, 1.05, and 1.19, nmol/l and 3.89, 2.71, and 2.24 nmol/l in non-asthmatic subjects (Figure 6.8). This blunted response was also reflected in lower plasma lactate levels of the asthmatic subjects when compared to the non-asthmatic subjects over the three testing protocols (Figures 6.10 - 6.12).

Table 7.2 Summary of major findings and recommendations from Study Three

Summary of Major Findings	Recommendations
1. No differences were found in the descriptive or maximal effort data between asthmatic and non-asthmatic subjects.	1. Extend the population base to improve the understanding of the exercise responses from various groups representing a range of maturational stages, severity of asthma and the training status of asthmatics.
2. Asthmatic and non-asthmatic subjects performed three high intensity cycle ergometer tests and displayed no significant differences between respective values for asthmatics and non-asthmatics for anaerobic performances of peak and mean power (watts).	2. Investigate a variety of intensities, durations and work rest ratios for any differences in performance and respiratory measures between EIA and non-asthmatic populations.
3. The asthmatics displayed blunted adrenaline and lactate levels following the high intensity tests compared with the non-asthmatic subjects.	3. Investigate the difference in timing when medication is withheld prior to testing.
4. The high intensity tests did not cause any FEV_1 reduction with asthmatic subjects.	4. Investigate: -oxygen kinetics through the breath by breath system -different environmental conditions on asthmatics during high intensity exercise -a variety of warm-up protocols before the high intensity exercise tests -high intensity running tests performed on either a treadmill or a field test involving distance over time.

In agreement with the previous two studies the first recommendation concerns focusing on the extension of the data base using populations with strong homogeneity. More specifically, it is recommended that further investigations be conducted to improve the understanding of the exercise responses from various groups representing a range of maturational stages, severity of asthma and the training status of asthmatics.

Recommendation two from this study focuses on an extension of the investigative protocol to broaden the understanding of young asthmatic subjects' responses to exercise. Designing studies with a variety of intensities, durations and work rest ratios to detect any differences in performance and respiratory measures between asthmatic and non-asthmatic populations would be valuable. For example protocols extending the total work time from 30 seconds up to 3 minutes involving supramaximal intensities may reflect a more realistic range of exercise demands likely to be encountered in popular physical pursuits. Because the present testing was performed on a cycle ergometer it would also be of value to investigate the responses during running-based activities. The issue of quantifying workload during treadmill protocols however, would need to be validated prior to investigations of this nature. One further concern within different exercise protocols with asthmatic populations is the nature and influence of the warm up implemented before high intensity exercise. For example a low intensity aerobic-based warm up may provoke greater bronchoconstriction than a more passive stretching regime.

One of the major findings in this study was an attenuated catecholamine response (adrenaline) in the asthmatic subjects when compared to their non-asthmatic counterparts following three different exercise protocols of high intensity. This finding contributes significantly to the current controversy surrounding the role of the sympathoadrenal responses in asthmatic populations.

The recommendation three calls for a stronger understanding of the sympathoadrenal responses from manipulations of the frequency and the dose of the β_2-agonists taken by subjects and time differences in withholding the medication. These factors appear to be crucial in quantifying accurate sympathoadrenal responses in asthmatics and they may explain some of the discrepancies within the literature.

The final recommendation from Study Three calls for investigations which vary in the type of equipment used for respiratory/metabolic analysis and the environmental conditions under which testing takes place. More sensitive measures for the assessment of oxygen kinetics may be obtained through the use of a breath by breath analysis system during both testing and recovery. Manipulations of differing but controlled environmental conditions on asthmatics during high intensity exercise would also contribute to the understanding of the asthmatic subject's responses to this type of exercise. For example high intensity running tests could be performed on a treadmill and then compared to those responses produced during field tests involving similar distances over time.

General Recommendations

The appropriate warm-up protocol is yet to be established in young asthmatics, considering that intermittent exercise sustained for six minutes in this study caused EIA. One of the strong recommendations from this study therefore, is to further investigate whether there is an appropriate warm-up protocol for asthmatics prior to exercise and whether asthmatics should pre-medicate prior to exercise. When examining the anaerobic performances of asthmatics compared to non-asthmatic subjects it is difficult to explain the abnormal responses within blood borne-indices. Further research investigating various medications and how they are administered (e.g. timing, type and quantity) may provide greater understanding of the mechanisms responsible for the blunted sympathoadrenal responses of asthmatics; in particular a study pertaining to the continual use of $ß_2$-agonist medication. As well as this recommendation, a study involving longitudinal design is required to explore the effects of maturational changes, performance characteristics and responses to medication among asthmatics.

Conclusion

The literature review on EIA highlighted the dearth of scientific attention previously given to homogenous populations of young people with EIA. There has been a distinct lack of research which has focused upon anaerobic metabolism and performance characteristics of the asthmatics during exercise. Controversy still remains regarding the causative mechanisms of EIA. This research has provided a broad foundation upon which the understanding of the anaerobic performance characteristics of young people with EIA can be based. Throughout each study that was conducted in this thesis an aged matched control group was used for a comparison with the asthmatic subjects. Previous research which had examined asthmatic subjects used subjects from diverse age ranges. A unique characteristic of the present research is the fact that for the first time all the subjects were closely matched for maturational status.

In all investigations in this thesis the groups displayed closely matched physical and maximal effort characteristics. Each of the three investigations implemented in this thesis provided exercise challenges which involved high intensity stimuli of an "anaerobic nature". The findings from each study highlighted that there were no performance based differences between the asthmatic and non-asthmatic subjects who volunteered for the respective studies. The results of performances are found to be contrary to previous postulations that asthmatics when compared to their non-asthmatics peers have diminished physical fitness (Bar-Or, 1986, Chryssanthopoulos et al., 1979, Clark and Cochrane, 1988, Ludwick et al., 1986, Varray et al., 1989). The young asthmatics from the three studies were able to produce high intensity performances at least equal to their non-asthmatic counterparts.

One of the crucial aspects of this research was the choice of an appropriate test to conduct in order to classify and diagnose the subjects as asthmatic. Consequently prior to each study the suspected asthmatic subjects were diagnosed by a provocation test to determine whether the subjects actually did respond positively with asthmatic symptoms. The hyperosmolar provocation test was used as a diagnosis for asthma in Study One, whereas in the latter two studies the six minute exercise provocation tests was employed for the diagnosis of asthma. The exercise challenge test is acknowledged as an appropriate test for the diagnosis of EIA as it provided a natural stimulus for the subjects. It would be recommended that future studies in the area of EIA should investigate a variety of different protocols for exercise challenge tests.

Limitations in previous studies that have displayed inferior aerobic and anaerobic performances may have been due to the variability in the sample tested. This study did however present differences in indices of

metabolic pathways between asthmatic and non-asthmatic subjects when blood-borne markers of high intensity exercise were investigated. Differences were particularly marked between measures of adrenaline in asthmatic and non-asthmatic volunteers in Study Three. It is difficult to explain the aforementioned results given the lack of differences in anaerobic performance data between the two groups. Findings of blunted levels in adrenaline have been previously demonstrated in other studies on asthmatic subjects (Barnes et al. 1981, Warren et al. 1982). There is however a lack of consensus on the sympathoadrenal responses to exercise in asthmatic subjects (Amirav et al., 1994, Berkin et al., 1988, Chryssanthopoulos et al. 1978, Hulks et al., 1991, Larsson et al., 1982, Zielinski et al., 1980). The mechanisms responsible for abnormal responses in asthmatics when compared to non-asthmatics remain uncertain. Further research involving blood-borne indices of anaerobic performances may therefore provide valuable insight into metabolic adaptations of young people with EIA.

Compared to continuous exercise, intermittent exercise proved to be equally as potent in the stimulus of bronchoconstriction in study two. This extends the contentious debate regarding the appropriate activities for exercise prescription for young EIA patients. Further investigations should explore the responses of asthmatics involving various types, intensities and timings of intermittent exercises with and without medication. An additional recommendation for future research would be to extend the different warm-up protocols that have been previously recommended for EIA athletes. The results of studies of this nature would suggest a very serious need for further research to determine whether intermittent exercise performed by asthmatic children should be promoted as a warm-up procedure. Previously it has been postulated that intermittent exercise as a warm-up protocol would help attenuate EIA. The conclusions of this study certainly would not support that postulation. The findings from study two strongly indicate a need to identify what is the appropriate prescribed warm-up or pre-medication for athletes with EIA. This study justified a necessity to further explore the responses that occur with short term exercise in asthmatics and the need to examine why the metabolic responses differ between asthmatic and non-asthmatic young populations.

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Appendix

Appendix A.1

STUDY 1

Dear Parents,

We are inviting your son to take part in a series of testing in the Exercise Physiology Laboratory at the Victoria University of Technology (Footscray campus). The purpose of the study is to investigate how much energy children use during very short but very intense running test on a treadmill.

It is proposed that the children will need to visit the laboratory seven times:

Visit 1:	Familiarisation session (equipment and procedures explained)
Visit 2:	A maximal effort running test where children have the speed increased every minute until they volunteer their exhaustion.
Visit 3-5	In these tests, children will perform a series of six sub-maximal tests with a duration of six minutes. They will do two tests per day allowing for at least 30 minutes rest between tests.
Visit 6-7	The children will be challenged to run for as long as they can at three different speeds which are harder than they have previously experienced.

Having conducted some of these tests last year on 10 to 12 year olds, we can assure you that the children really enjoyed the tasks and performed them extremely well. The children also benefited from the visits to the laboratory in that many experiences were very interesting to them. Although with this type of research there is the potential of having mild asthma, a physician will be present throughout the test and ventolin medication will

be given if needed.. Throughout all the tests consistent positive reinforcement is given to encourage the child to do his best. Following each test the child receives an orange juice and a health bar.

Appendix A.1

We are seeking permission for your son to partake in the testing at Victoria University of Technology and to transport him to and from the laboratory in my car (DEE 413). For all testing, shorts and runners are preferred. Since the previous group of children performed much better in the morning, it has been decided to ask whether the children can be picked up at 8:45 a.m. and returned to the school at approximately Noon. All testing will be conducted on Monday, Wednesday, and Friday mornings.

I permit my child to be transported by car (DEE 413) and to take part in the testing at Royal Children's Hospital.

(PARENT) SIGNED_____ DATE:_____

(CHILD) SIGNED_____ DATE:_____

Appendix A.2

STUDY 2

Dear Parents, 30/5/94

We are inviting your child to take part in a series of testing in the Thoracic Medicine Department at the Royal Children's Hospital. The purpose of this study is ***to examine the influence of repetitive, high intensity work on children with exercise induced asthma***

Having conducted some of these tests last year and early this year on 10 to 12 year olds, we can assure you that the children really enjoyed the tasks and performed them extremely well. The children also benefited from the visits to the laboratory in that many experiences were very interesting to them and appeared to be learning a great deal about their body's response to exercise and asthma. Although with this type of research there is the potential of having mild asthma, a physician will be present throughout the test and ventolin medication will be given if needed.

Chidren are required to withhold asthma medication eight hours prior to each testing visit. Children will also be required to complete a standard questionnaire concerning current therapy and asthma status. Commonly accepted lung function screening tests will be conducted throughout all exercise procedures within the Thoracic Medicine Dept. of the hospital. This consists of standard spirometry tests to ensure that the lung function is satisfactory. The general aim of the project and specific requirements of the subject will be explained to the subject at this time on the first visit. On subsequent visits the specific requirement of that testing session will be explained

Visit 1: Performance of a VO_2 max test

This test is critical to allow individual determination of treadmill work load settings required for the future experimental visits. In addition this test will provide a good introduction for the subject to the laboratory environment and to assess the general exercise tolerance of the subject.

Appropriate instruction about the test and practice at running on the treadmill will also be provided. Prior to testing, it will be made clear to the subject that the test may be stopped at any time by the subject's own volition.

Appendix A.2

Visit 2-5 - Test protocols

On visit 2 the subject will complete a standard 6 minute treadmill continuous exercise test, at a work rate - that is calculated from the VO2 peak test to require a HR of 170-180bpm. This test is designed to provoke a maximal EIA response. In addition, 4 other tests will be carried out where the subject is required to do the same amount of work as in the continuous test, within the same total time period where the work is intermittent. The four test protocols listed below are to be completed by the subjects according to a randomised order. The four work/rest regimes are as follows:

	EXAMPLE
A.6 min continuous	5 kph treadmill continuous run for 6min
B. Work 15s, Rest 15s, intensity 2xA for 6min.	10kph run for 15 sec. rest 15 sec. for 6 min
C.Work 30s, Rest 30s, intensity 2xA for 6min.	10kph run for 15 sec. rest 15 sec. for 6min
D. Work 15s, Rest 30s, intensity 3xA for 6min.	15kph run for 15 sec. rest 30 sec. for 6 min

We are seeking permission for your child to partake in the testing at the Royal Childrens Hospital and to transport him to and from the laboratory in my car (DEE 413). For all testing, shorts and runners are preferred. Since the previous group of children performed much better in the morning, it has been decided to ask whether the children can be picked up at 8:45 a.m. and returned to the school at approximately Noon. All testing will be conducted on Monday, Wednesday, and Friday mornings.

Conditions granted for school excursions and in particular school medical consent forms will apply throughout the testing.

Your co-operation is valued.

David Buttifant Rick Roberts Prof. John Carlson

PH.688-4093 PH.345-5841 PH.688-4385

Appendix A.3

STUDY 3

Dear Parents,

We are inviting your child to take part in a series of testing in the Exercise Physiology Laboratory, Department of Physical Education and Recreation Victoria University of Technology. The purpose of this study is ***to examine the influence of high intensity work on children with exercise induced asthma***

Having conducted some of these tests early this year, we can assure you that the boys really enjoyed the tasks and performed them extremely well. The boys also benefited from the visits to the laboratory in that many experiences were very interesting to them and they appeared to be learning a great deal about their responses to exercise..

The general aim of the project is to investigate the effects of high intensity exercise on asthmatics and to compare their results with non asthmatics. The specific requirements of the subject will be explained to the subject on the first visit. On subsequent visits the specific requirement of that testing session will be explained. There will be a total of four visits to the laboratory on separate days which involves approximately three hours per session.

Visit 1: Performance of a VO_2 max test

This test will provide a good introduction for the subject to the laboratory environment and to assess the general exercise tolerance of the subject. Prior to testing, it will be made clear to the subject that the test may be stopped at any time by the subject's own volition. All tests will be performed on a stationary cycle ergometer.

Visit 2: 30 second Wingate test Protocol

This test assesses the characteristics of anaerobic performance and is perceived as a reliable test for peak power and mean power over 30 seconds. The subject will perform basic Lung Function Tests.

. An indwelling catheter will be inserted into the intermediate antebrachial vein of a pre-warmed forearm while the subject is in a supine position. The venous catherization will be conducted by a trained phlebotomist member of the research team.

Appendix A.3

Visit 3: 2X15 Second Wingate test Protocol B

Visit 4: 3X10 Second Wingate test Protocol C

Although with this type of research there is the potential of having asthma, a physician will be present throughout the test and ventolin medication will be given if needed. We are seeking permission for your child to partake in the testing at Victoria University of Technology and to transport him to and from the laboratory in my car (EFI 625). For all testing, shorts and runners are preferred. Since the previous group of children performed much better in the morning, it has been decided to ask whether the children can be picked up at 8:45 a.m. and returned to the school at approximately Noon.
Conditions granted for school excursions and in particular school medical consent forms will apply throughout the testing.

Your co-operation is valued.

David Buttifant
PH.688-4093

Prof. John Carlson
PH.688-4385

Appendix A4

RESPIRATORY SYMPTOMS SURVEY

Please fill the details below, then complete the questionnaire carefully and accurately. All replies will be treated with complete confidentiality.

CHILD'S NAME_____

DATE OF BIRTH_____SEX_____

RELATIONSHIP TO CHILD OF PERSON COMPLETING FORM_____

RESPIRATORY QUESTIONNAIRE

All the questions ask you to answer by placing a tick in the appropriate square. For example:

YES ☐ NO ☐ DON'T KNOW ☐

1. Has your child had wheezing or whistling in the chest at any time in the past?

YES ☐ NO ☐ DON'T KNOW ☐

2. Has your child ever had asthma?

YES ☐ NO ☐ DON'T KNOW ☐

3. In the last 12 months, has your child had a wheezing or asthma attack?

YES ☐ NO ☐ DON'T KNOW ☐

4. In the last 12 months, how frequent were the wheezing or asthma attacks?

None in the last 12 month	☐
Less than 4 attacks	☐
4 to 12 attacks	☐
More than 12 attacks	☐

5. In the last 12 months, has any wheezing or asthma attack woken your child at night?

YES ☐ NO ☐ DON'T KNOW ☐

6. In the last 12 months, has any wheezing or asthma attack been severe enough to limit speech to only one or two words at a time between breaths?

YES ☐ NO ☐ DON'T KNOW ☐

7. In the last 12 months, has your child sounded wheezy during or after exercise?

YES ☐ NO ☐ DON'T KNOW ☐

8. In the last 12 months, has your child had a dry cough at night? (Apart from a cough associated with a cold or chest infection.)

YES ☐ NO ☐ DON'T KNOW ☐

9. In the last 12 months, has your child usually brought up any phlegm or mucous from the chest first thing in the morning?

YES ☐ NO ☐ DON'T KNOW ☐

10. In the last 12 months, has your child woken with feeling of tightness in the chest first thing in the morning?

YES ☐ NO ☐ DON'T KNOW ☐

11. In the last 12 months, has your child had tightness in the chest or become short of breath when near animals, feathers or dust?

YES ☐ NO ☐ DON'T KNOW ☐

12. In the last 12 months, has your child been treated at any time with any of the following medications?

Ventolin	Bricanyl	Nuelin	Somophyllin
Respolin	Berotec	Theodor	Elixophyllin
			Slo-bid

YES ☐ NO ☐ DON'T KNOW ☐

AT ANY TIME IN THE PAST:

13. Has your child ever suffered from bronchitis?

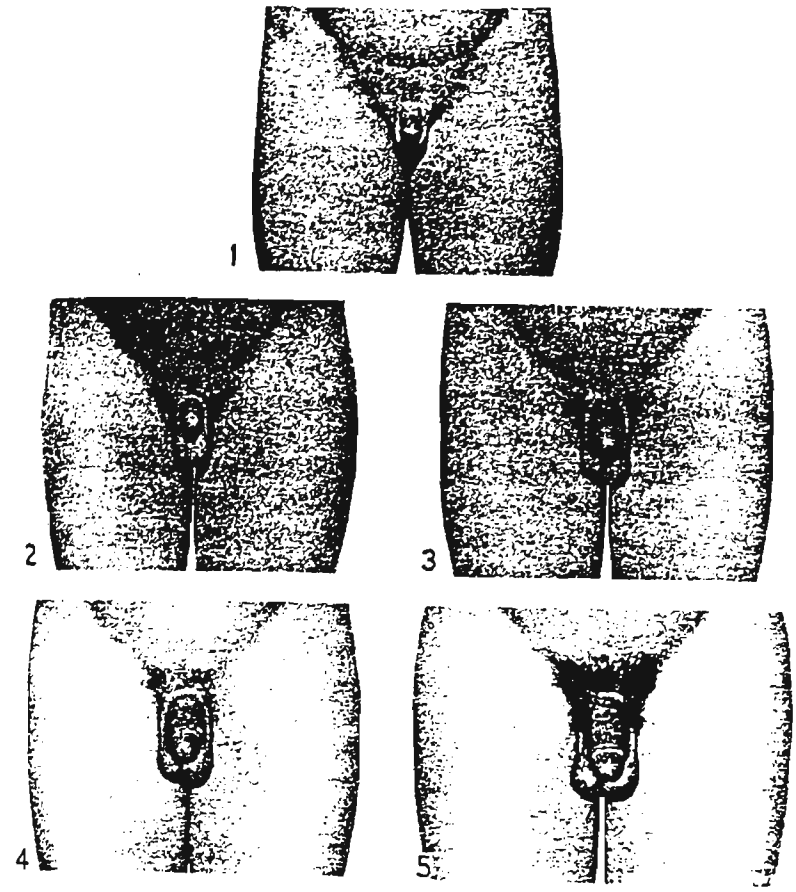
YES ☐ NO ☐ DON'T KNOW ☐

14. Has your child ever suffered from wheezing with bronchitis or with a cold?

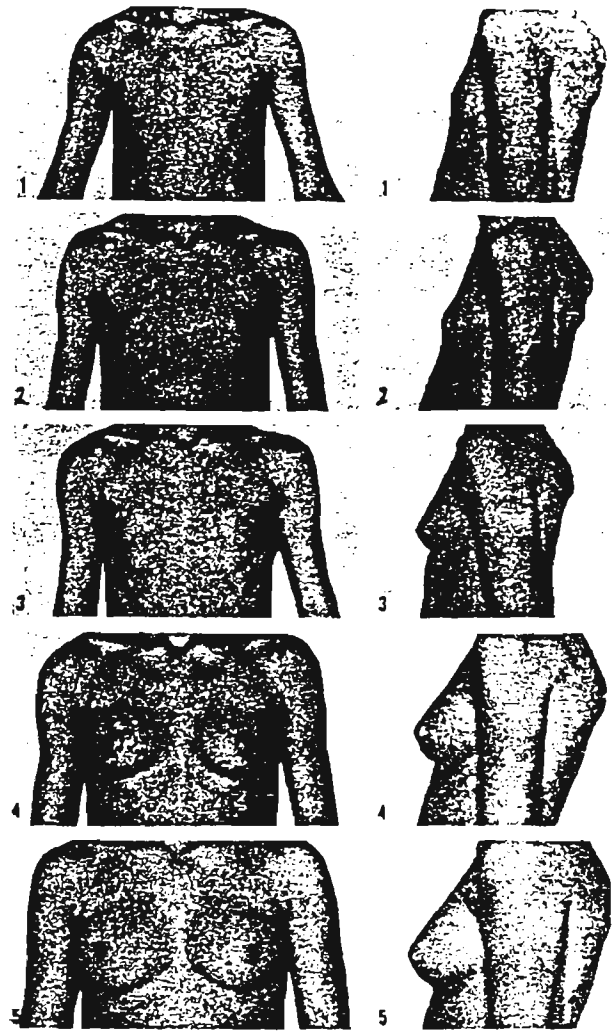
YES ☐ NO ☐ DON'T KNOW ☐

Thank you for taking the time to answer these questions. Please check carefully that you have not missed anything.

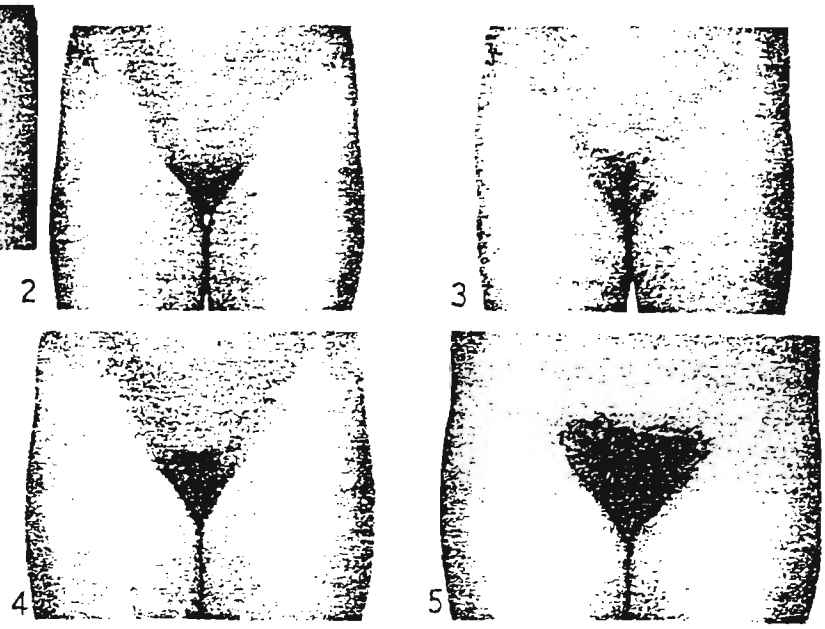
Appendix B Tanner Scale Maturation Stages of Development



Genitalia standards



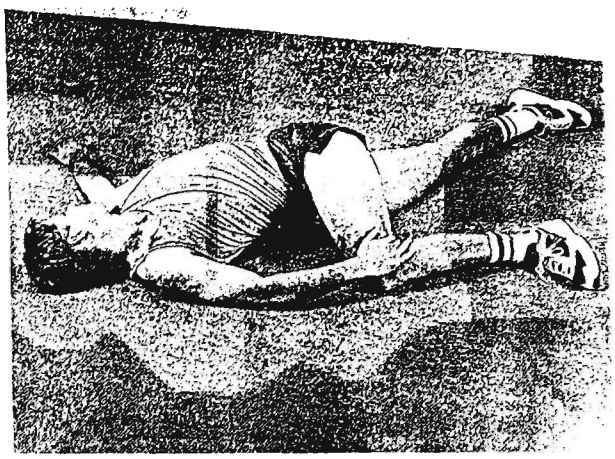
Breast standards



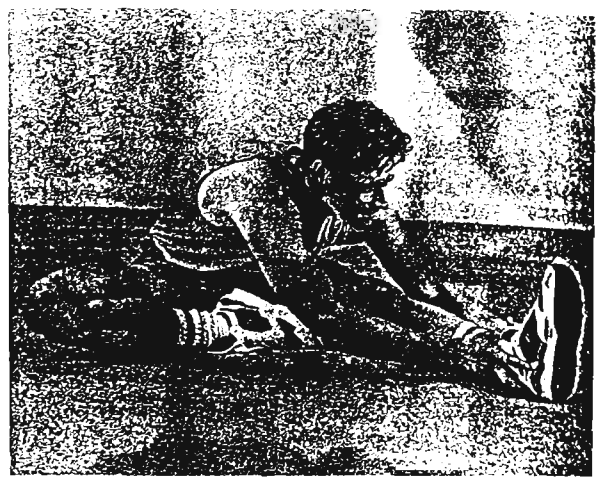
Pubic hair standards

(from Tanner, 1962)

Appendix C



Lower back and hip stretch.



Hamstring stretch

Quadriceps stretch

Groin stretch

Calf stretch.

Appendix D

Sample of the methodology used to obtain accumulated oxygen deficit values.

Subject "Gerard", Age = 10.7 years Body Mass = 35.50

VO_2 max = 53.39 ml.kg $^{-1}$·min $^{-1}$

Steady State responses

Workload (kph)	VO_2 (ml.kg $^{-1}$·min $^{-1}$)
6	37.39
6.25	39.27
7	41.40
7.25	42.66
7.5	43.98
8	46.64

Linear regression from steady state data

y = a + b (x)

y = 11.57 + 4.33 (speed)

r = .9913

Supramaximal predictions

Max VO_2 = 53.39 ml.kg $^{-1}$·min $^{-1}$ Supramaximal VO_2 for 130% = 69.41 ml.kg $^{-1}$·min $^{-1}$

Predicted speed for 130% intensity =

Sample of calculations for AOD

Time to exhaustion = 69.4 s (= 1.23 min.)

Predicted O_2 for time = 68.73 (ml.kg $^{-1}$·min $^{-1}$) x 1.23 (min.)

Σ= 84.54 (ml.kg $^{-1}$)

Actual O_2 for time = 34.20(ml.kg $^{-1}$·min $^{-1}$) x 1.23 (min.)

Σ= 42.06 (ml.kg $^{-1}$)

Accumulated O_2 deficit = Predicted O_2 for time - Actual O_2 for time

=84.54 - 42.06

= 42.06 (ml.kg $^{-1}$)

APPENDIX E 1.1 STUDY ONE
FACTORIAL ANALYSIS

CONDITION = ASTHMATIC AND NON-ASTHMATIC

ANALYSIS OF VARIANCE

Variable **HEIGHT**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	2.7011	2.7011	0.0492	0.8269
Within Groups	18	987.6803	54.8711		
	19	990.3814			

By Variable **AGE**
CONDITION

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	65.8119	65.8119	1.2991	0.2693
Within Groups	18	911.8965	50.6609		
	19	977.7084			

Variable **MASS**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	0.0042	0.0042	0.031	0.8623
Within Groups	18	2.4446	0.1358		
	19	2.4489			

Variable **PEAK RER DURING VO2 MAX TEST**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	0.0068	0.0068	2.0248	0.1718
Within Groups	18	0.0608	0.0034		
	19	0.0677			

Variable **PEAK HR DURING PEAK VO2 MAX**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	156.8	156.8	5.4444	0.0314
Within Groups	18	518.4	28.8		
	19	675.2			

Variable **PEAK VO2 ML.KG.MIN-1**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	149.6045	149.6045	3.483	0.0784
Within Groups	18	773.1509	42.9528		
	19	922.7554			

APPENDIX E 1.2 STUDY ONE
FACTORIAL ANALYSIS

Variable **BTPS DURING VO2 PEAK TEST**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	82.0935	82.0935	0.8145	0.3787
Within Groups	18	1814.1539	100.7863		
	19	1896.2474			

Variable **O2 DEFICIT ML. KG**
By Variable **CONDITION AND TEST**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	3	205.2485	68.4162	0.6362	0.5966
Within Groups	36	3871.6248	107.5451		
	39	4076.8733			

Variable **O2 DEFICIT LITRE**
By Variable **CONDITION AND TEST**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	3	1.3049	0.435	1.294	0.2913
Within Groups	36	12.101	0.3361		
	39	13.406			

Variable **RER110**
By Variable **CONDITION AND TEST**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	3	0.0127	0.0042	1.0025	0.4029
Within Groups	36	0.1524	0.0042		
	39	0.1651			

Variable **SPEED KPH** **TEST = 110 &130%**
By Variable **CONDITION AND TEST**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	3	64.1684	21.3895	8.1765	0.0003
Within Groups	36	94.175	2.616		
	39	158.3434			

Variable **HR**
By Variable **CONDITION AND TEST**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	3	289.4	96.4667	2.2145	0.1032
Within Groups	36	1568.2	43.5611		
	39	1857.6			

APPENDIX E 1.3 STUDY ONE
FACTORIAL ANALYSIS

Variable **TIME TO EXHAUSTION**
By Variable **CONDITION AND TEST**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	3	70408.77	23469.59	16.0646	0.0001
Within Groups	36	52594.157	1460.9488		
	39	123002.93			

Variable **BTPS**
By Variable **CONDITION AND TEST**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	3	156.3086	52.1029	0.4803	0.698
Within Groups	36	3905.4713	108.4853		
	39	4061.7799			

% CHANGE IN FEV1 RESPONSES FOLLOWING 110 AND 130% TEST

REPEATED MEASURES DESIGN	SS	DF	MS	F	Sig of F
WITHIN+RESIDUAL	1684.27	90	18.71		
	124.15	5	24.83	1.33	0.26
TREAD BY FACTOR1	21.54	5	4.31	0.23	0.948

APPENDIX E 2.1 STUDY TWO
FACTORIAL ANALYSIS
CONDITION = ASTHMATIC AND NON-ASTHMATIC

Variable **AGE**
By Variable **CONDIT**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	0.1716	0.1716	0.4701	0.5028
Within Groups	16	5.841	0.3651		
Total		17	6.0126		

Variable **MASS**
By Variable **CONDIT**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	0.3004	0.3004	0.0082	0.929
Within Groups	16	586.469	36.6543		
Total		17	586.7694		

Variable **HT**
By Variable **CONDIT**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	4.7295	4.7295	0.1071	0.7477
Within Groups	16	706.6498	44.1656		
Total		17	711.3793		

Variable **BMI**
By Variable **CONDIT**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	1.0081	1.0081	0.1221	0.7313
Within Groups	16	132.0728	8.2545		
Total		17	140.25		

Variable **VO2PEAK**
By Variable **CONDIT**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	34.7512	34.7512	0.971	0.3391
Within Groups	16	572.6512	35.7907		
Total		17	607.4024		

Variable **VO2 MAX TEST RER**
By Variable **CONDIT**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	0.0176	0.0176	7.2724	0.0159
Within Groups	16	0.0388	0.0024		
Total		17	0.0565		

APPENDIX E 2.2 STUDY TWO
FACTORIAL ANALYSIS

GROUPS = CONT. & INTERMITTENT PROTOCOLS
CONDITION = ASTHMATIC AND NON-ASTHMATIC

VO2 MAX TEST PEAK
HR
By Variable **CONDIT**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	1.7361	1.7361	0.0705	0.794
Within Groups	16	393.875	24.6172		
Total		17	395.6111		

Variable **VO2 MAX TEST VE**
By Variable **CONDIT**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	664.475	664.475	22.4399	0.0002
Within Groups	16	473.7804	29.6113		
Total					

Variable **HR**
By Variable **GROUPS**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	1.7361	1.7361	0.0705	0.794
Within Groups	16	393.875	24.6172		

Variable **VO2**
By Variable **GROUPS**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	34.7512	34.7512	0.971	0.3391
Within Groups	16	572.6512	35.7907		
	17	607.4024			

Variable **VE**
By Variable **GROUPS**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	6.8857	6.8857	0.3666	0.5534
Within Groups	16	300.5148	18.7822		
	17	307.4005			

Variable **RER**
By Variable **GROUPS**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	0.0001	0.0001	0.0544	0.8185
Within Groups	16	0.0295	0.0018		
	17	0.0296			

APPENDIX E 2.3 STUDY TWO
FACTORIAL ANALYSIS
GROUPS = CONT. & INTERMITTENT PROTOCOLS
CONDITION = ASTHMATIC AND NON-ASTHMATIC

Variable **RPE Breathing**
By Variable **GROUPS**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	182.40	11.40	1.72	0.208
Within Groups	16	19.60	19.60		

Variable **RPE local muscular fatigue**
By Variable **GROUPS**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	191.10	11.94	.32	0.580
Within Groups	16	3.80	3.80		

Variable **FEV1 REDUCTION**
By Variable **GROUPS**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	4417.0028	4417.0028	55.9657	0.0001
Within Groups	16	1262.775	78.9234		
	17	5679.7778			

APPENDIX E3.1 STUDY THREE
FACTORIAL ANALYSIS

CONDITION = ASTHMATIC AND NON-ASTHMATIC

Variable **AGE**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	1.3224	1.3224	2.3077	0.1452
Within Groups	19	10.8879	0.573		
	20	12.2103			

Variable **BMI**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	0.1302	0.1302	0.0178	0.8953
Within Groups	19	138.9593	7.3136		
	20	139.0895			

Variable **HEIGHT**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	22.8407	22.8407	0.5608	0.4631
Within Groups	19	773.8374	40.7283		
	20	796.6781			

Variable **MASS**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	71.8488	71.8488	0.5784	0.4563
Within Groups	19	2360.1631	124.2191		
	20	2432.0118			

Variable **TESTOSTERONE**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	111.3065	111.3065	0.0515	0.8229
Within Groups	19	41068.979	2161.5252		
	20	41180.286			

Variable **VO2MAX (ml.kg-1.min-1)**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	9.7208	9.7208	0.5475	0.4684
Within Groups	19	337.3593	17.7558		
	20	347.0801			

APPENDIX E3.2
STUDY THREE
FACTORIAL ANALYSIS

CONDITION = ASTHMATIC AND NON-ASTHMATIC

Variable **MVV**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	571.38	571.38	2.5504	0.1277
Within Groups	19	4032	224.031		
	20	4603.94			

Variable **SKINFOLDS**
By Variable **CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	1	38.4175	38.4175	0.2753	0.6058
Within Groups	19	2651.0054	139.5266		
	20	2689.4229			

Variable **ASTHMATICS PEAK PERCENTAGE REDUCTION OF FEF25-75% FOLLOWING THE THREE HIGH INTENSITY TESTS**
By Variable TESTS

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	2	34.9047	17.4523	0.1988	0.8209
Within Groups	27	2370.5679	87.7988		
	29	2405.4725			

Variable **PEAK POWER (watts)**
By Variable TESTS & CONDITION

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	5	10150.034	2030.0067	0.1408	0.982
Within Groups	57	821611.24	14414.232		
	62	831761.27			

Variable **RELATIVE PEAK POWER (w.kg-1)**
By Variable TESTS & CONDITION

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	5	0.6623	0.1325	0.0519	0.9982
Within Groups	57	145.4907	2.5525		
	62	146.1529			

Variable **MEAN POWER (watts)**
By Variable TESTS & CONDITION

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	5	17705.1	3541.0201	0.3554	0.8767
Within Groups	57	567989.83	9964.7339		
	62				

APPENDIX E3.3
STUDY THREE
FACTORIAL ANALYSIS

Variable **RELATIVE MEAN POWER (w.kg-1)**
By Variable **TESTS & CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	5	4.7671	0.9534	0.5272	0.7547
Within Groups	57	103.0795	1.8084		
	62	107.8466			

Variable **MEAN VENTILATION**
By Variable **TESTS & CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	5	3716.9999	743.4	3.3035	0.0109
Within Groups	57	12826.893	225.0332		
	62	16543.893			

Variable **PEAK HR**
By Variable **TESTS & CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	5	475.6356	95.1271	1.6428	0.1635
Within Groups	57	3300.6818	57.9067		
	62	3776.3175			

Variable **MEAN VO2 ml.kg.min-1**
By Variable **TESTS & CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	5	263.4236	52.6847	1.8492	0.1178
Within Groups	57	1624.0044	28.4913		
	62	1887.428			

Variable **RER**
By Variable **TESTS & CONDITION**

Source	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Between Groups	5	0.0848	0.017	3.7021	0.0057
Within Groups	57	0.2612	0.0046		
	62	0.3461			

REPEATED MEASURES **ADRENALINE**
TESTS & CONDITION

	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Within + residual	80	114.64	1.43		
Tests	5	97.59	19.52	13.62	.0001
Condition by tests	5	19.30	3.86	2.69	.027

APPENDIX E3.4
STUDY THREE
FACTORIAL
ANALYSIS

REPEATED MEASURES **NOR-ADRENALINE TESTS & CONDITION**

	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Within + residual	85	344.12	4.05		
Tests	5	1066.30	213.26	52.68	.0001
Condition by tests	5	40.64	8.13	2.01	.086

REPEATED MEASURES **LACTATE TESTS & CONDITION**

	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Within + residual	266	991.74	3.73		
Tests	14	2677.64	191.26	51.30	.0001
Condition by tests	14	113.02	8.07	2.17	.009

REPEATED MEASURES **pH TESTS & CONDITION**

	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Within + residual	266	.41	.001		
Tests	14	1.19	.08	55.53	.0001
Condition by tests	14	.03	.001	1.27	.226

REPEATED MEASURES **HCO_3 TESTS & CONDITION**

	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Within + residual	266	2986.41	11.23		
Tests	14	3669.51	262.11	23.35	.0001
Condition by tests	14	174.82	12.49	1.11	.347

REPEATED MEASURES **Hb TESTS & CONDITION**

	D.F.	Sum of Squares	Mean Squares	F Ratio	F Prob.
Within + residual	266	186.35	.70		
Tests	14	72.05	5.15	23.35	.0001
Condition by tests	14	8.45	12.49	1.11	.347

APPENDIX E3.4 STUDY THREE

Mean pH, HCO_3 and Hb values before and following high intensity tests

	1 x 30				2 x 15				3 x 10			
	A		NA		A		NA		A		NA	
pH												
pre	7.35	(0.01)	7.36	(0.02)	7.35	(0.01)	7.36	(0.02)	7.37	(0.01)	7.38	(0.01)
1min	7.21	(0.02)	7.20	(0.02)	7.17	(0.02)	7.18	(0.02)	7.21	(0.01)	7.20	(0.03)
3 min	7.20	(0.01)	7.21	(0.02)	7.17	(0.02)	7.19	(0.01)	7.21	(0.01)	7.20	(0.02)
6 min	7.21	(0.01)	7.20	(0.01)	7.18	(0.02)	7.20	(0.01)	7.21	(0.01)	7.22	(0.01)
12 min	7.24	(0.01)	7.22	(0.01)	7.22	(0.02)	7.21	(0.02)	7.24	(0.01)	7.24	(0.02)
HCO_3 (mmol/L)												
pre	25.71	(0.47)	26.27	(1.21)	25.02	(0.77)	27.26	(1.51)	24.60	(1.10)	26.52	(0.55)
1min	19.96	(1.05)	21.30	(1.92)	18.62	(1.04)	20.90	(1.99)	17.75	(1.05)	19.85	(1.35)
3 min	17.40	(0.86)	19.94	(2.47)	16.54	(1.00)	20.31	(2.31)	15.35	(0.53)	18.53	(1.41)
6 min	15.71	(0.64)	20.62	(2.37)	15.06	(0.82)	20.44	(2.28)	14.48	(0.45)	16.95	(1.22)
12 min	15.60	(0.74)	21.22	(2.53)	14.99	(0.88)	21.15	(2.45)	14.84	(0.46)	17.11	(0.92)
Hb (g/dl)												
pre	14.57	(0.32)	14.44	(0.37)	15.24	(0.25)	14.70	(0.37)	14.32	(0.45)	14.66	(0.35)
1min	15.15	(0.39)	15.71	(0.23)	15.76	(0.29)	15.81	(0.34)	15.34	(0.48)	15.85	(0.29)
3 min	15.74	(0.41)	15.66	(0.24)	16.11	(0.23)	15.85	(0.33)	16.09	(0.35)	16.05	(0.34)
6 min	15.46	(0.35)	15.51	(0.27)	16.10	(0.22)	15.74	(0.31)	15.93	(0.32)	15.97	(0.37)
12 min	15.43	(0.33)	15.35	(0.24)	15.98	(0.23)	15.34	(0.29)	15.69	(0.34)	15.73	(0.37)

M±SEM

A = Asthmatics

N =Non asthmatics