PREVALENCE, DIAGNOSIS AND TREATMENT OF EXERCISE INDUCED ASTHMA IN ELITE ATHLETES

A thesis submitted for the degree of Doctor of Philosophy awarded by Brunel University

by

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February 2006

Abstract

An acute asthmatic episode can occur following exercise and is termed exercise induced asthma (EIA). The purpose of this thesis was to investigate the prevalence, diagnosis, and treatment of EIA in elite British athletes.

The addition of objective pulmonary function assessment to the criteria an athlete must submit to use inhaled β_2-agonists at Olympic Games may result in a change in the prevalence of asthma within elite athletes. The purpose of study 1 was to compare the prevalence of asthma at the 2000 and 2004 Olympic Games in the Great British Olympic team (Team GB). The asthma prevalence of Team GB reported in 2000 (21.2%) was similar to the asthma prevalence reported in 2004 (20.7%). 13 out of 62 (21.0%) athletes, from 2004 Team GB with a previous diagnosis of asthma failed to present evidence of EIA. The overall asthma prevalence of Team GB remained unchanged between 2000 and 2004.

Mid-expiratory airflow measurements may improve the diagnosis of EIA in elite athletes. Study 2 investigated the response of Forced Expiratory Flow at 50% vital capacity (FEF_{50}) following eucapnic voluntary hyperpnoea (EVH) and exercise challenge, in elite athletes, as an adjunct to Forced Expiratory Volume in one second (FEV_1). 66 male and 50 female athletes were tested for EIA. Sixty athletes demonstrated a fall in FEV_1 $\geq$10% leading to the diagnosis of EIA. Using the FEF_{50} criteria (ΔFEF_{50} $\geq$-26%) led to 21 (35%) asthmatic athletes receiving false negative diagnosis. The addition of FEF_{50} failed to enhance the diagnosis of EIA in elite athletes.

It is unclear, between exercise and EVH challenges as to which one provides the greatest sensitivity and most suitable method of EIA diagnosis in elite athletes. Study 3 investigated the response of elite winter athletes to EVH and two exercise challenges (laboratory-based [LB] and sport-specific [SS]). 14 athletes from the British Short-track Speed Skating and Biathlon teams volunteered for the study. Ten athletes presented with a positive response to EVH (71%); of these, only 3 (21%) had a positive response to the SS challenge. No athletes had a positive test to the LB challenge. Our results suggest that the EVH challenge is more sensitive, compared with either LB or SS exercise challenge, to diagnose EIA in elite winter athletes.

A limited number of studies exist examining the optimal pharmacotherapy for elite athletes with EIA. The purpose of study 4 was to examine the effects of fluticasone propionate and salmeterol in the control of EIA in athletes. Eight athletes were prescribed 200mcg fluticasone propionate (FLU), 50mcg Salmeterol (SAL), 250mcg fluticasone propionate and salmeterol in combination (FXS) or placebo (PLA), in a randomised double blind design. No significant ($p=0.07$) differences were observed in the FEV_1 change (ΔFEV_1) following EVH challenge between the 4 treatments. Baseline eNO for both FXS (20.3$\pm$8.2ppb) and FLU (19.7$\pm$9.2 ppb) were significantly ($p=0.02$) lower than SAL (39.3$\pm$26.7ppb) or PLA (46.3$\pm$26.8ppb). Four athletes were prescribed FLU, 2 athletes were prescribed FXS and 2 athletes were prescribed SAL. The results of this study demonstrate the heterogeneity of response in elite athletes with EIA to the three medication regimes employed. Therefore, suggesting differences in the pathogenesis of EIA in this population.

This thesis is the first to investigate EIA within elite British athletes. The prevalence of asthma within elite athletes is greater than that of the British general population. Optimal EIA diagnostic methods should include EVH challenges using FEV_1 as the criterion measurement. Treatment for athletes with EIA should be taken on an individual basis due to the heterogeneity of response to medications that attenuate EIA in elite athletes.

Acknowledgements

I would like to thank my supervisors Professor Alison McConnell and Professor Greg Whyte for their initial belief in me and continuous support. In addition Dr Mark Harries has provided significant guidance and advice.

This work would not have been possible without all the participants who have taken part in this thesis. It was a joy and pleasure to work with so many talented individuals from all sporting disciplines.

The Olympic Medical Institute and English Institute of Sport have been a great support. In particular I would like to thank those who have assisted in the organisation of testing dates, timetabling of athletes and providing their own pair of hands whenever it was requested. I would also like to thank Micro Medical for the donation of 4 spirometers and technical assistance.

Mum and Dad have been great!

My wife Rebecca has been superb. Without her support and continuous love this thesis would not have been possible.

I would also like to thank all those who have been a part of my education: Whitby Heath Primary School, Stanney High School, Bangor University and Brunel University.

Live the dream

Abbreviations

EIA	Exercise Induced Asthma
IOC-MC	International Olympic Committee – Medical Commission
IBAs	Inhaled beta-2-agonists
EVH	Eucapnic Voluntary Hyperpnoea
FEV_1	Forced Expiratory Volume in one Second
FVC	Forced Vital Capacity
PEF	Peak Expiratory Flow
FEF_{50}	Forced Expiratory Flow at 50% vital capcity
FEF_{25-75}	Average of Forced Expiratory Flow between 25% and 75% of vital capacity
β_2-agonists	Beta-2-agonists
Δ	Maximum change from baseline measurement
ΔFEV_1	Maximum fall from baseline measurement of FEV_1
SCF	Stem Cell Factor
IL	Interleukin
IgE	Immoglobulin E
O_2	Oxygen
CO_2	Carbon Dioxide
N_2	Nitrogen
ATS	American Thoracic Society
BTS	British Thoracic Society
LB	Laboratory Based
SS	Sports Specific
$FEV_1\%$	The percentage of FVC expired in the first second

ANOVA	Analysis of Variance
eNO	Exhaled Nitric Oxide
FXS	Fluticasone Propionate and Salmeterol
FUL	Fluticasone Propionate
SAL	Salmeterol
$\dot{V}_E$	Minutes Ventilation
MVV	Maximum Minute Ventilation
PUFA	Polyunsaturated Fatty Acids
UIB	Unexplained Inappropriate Breathlessness

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Chapter 1

Introduction

Asthma is an obstructive condition that results in a reduced expiratory airflow, within susceptible individuals, that is reversible with appropriate therapy or spontaneously. The pathophysiology of asthma is not entirely understood, however, airflow limitation is thought to be the result of airway smooth muscle contraction and inflammation. A number of inflammatory mediators including cytokines, prostaglandins, leukotrienes, histamine and eicosanoids from mast cells and macrophages are thought to be key contributors to acute asthma episodes. Prolonged exposure to these inflammatory mediators (e.g. from multiple acute EIA episodes) can lead to an increased mast cell survival rate and a reduction in apoptosis within the airways, which may lead to the development of chronic inflammation and airway remodelling. It is therefore important that individuals who suffer from acute episodes of asthma receive correct diagnosis and suitable therapy to control asthma and prevent the potential airway remodelling and increases in asthma severity.

An acute asthmatic episode can occur following exercise and is termed exercise induced asthma (EIA). EIA is defined as a transient narrowing of the airways following exercise and is present in approximately 80-90% of people with asthma (Anderson, 1997). Exercise is a trigger for approximately 90% of all asthmatics and may be the only trigger for those with mild asthma. As with asthma, the pathophysiology of EIA is not fully understood. It is thought however, to be caused by water loss from the small airways, which is due to an increase in the volume of 'unconditioned' air entering the

smaller airways during exercise (Anderson and Daviskas, 2000; Anderson and Kippelen, 2005). This explanation of EIA pathophysiology is known as the osmotic hypothesis and is based around the understanding that an increase in osmolarity produces a favourable environment for mediators to be released, which causes the smooth muscle surrounding the airways to contract, limiting expiratory air flow. Furthermore, other cells such as mast cells, eosinophils, macrophages and sensory nerve cells can potentially be subjected to cell volume loss (figure 2.6). Inflammatory mediator release is stimulated by the regulatory volume increase, after cell shrinkage (Anderson and Daviskas, 2000). Strauss et al. (1978) and Anderson et al. (1982) reported the severity of EIA is directly proportional to the water content of inspired air and the water loss at the mouth. In addition, they noted that when water loss was prevented, so to was EIA, even in severe asthmatics. As EIA can occur without significant cooling, the osmotic effects are thought to be more important than thermal effects (Anderson and Daviskas, 1993; Evans et al., 2005). It is therefore generally accepted that the osmotic hypothesis accommodates the established findings regarding the pathophysiology of EIA and asthma.

The prevalence of asthma within the general population of the UK is 8% (Asthma UK, 2001). In contrast, the prevalence of asthma/EIA within elite athletic populations has been reported to be between 11-50% (Voy, 1986; Wilber et al., 2000), depending on the type of sport studied. It therefore appears that asthma prevalence is higher in athletic populations compared with the general population. Reports within literature on the prevalence of asthma/EIA within national Olympic squads are limited. The United States of America (USA) first reported the prevalence of asthma within their 1984 Olympic squad to be 11% (Voy, 1986). Further reports from the USA Olympic teams

have demonstrated that the prevalence of asthma has risen to 14% at the 1996 Atlanta Olympic Games (Weiler et al., 1998) and 17% at the 1998 Nagano Winter Olympic Games (Weiler and Ryan, 2000). Whilst there seems to be a progressive rise in EIA within the USA Olympic teams, there are limited reports of asthma prevalence from other nations' Olympic teams. What remains unclear is whether the observed increase in the prevalence of asthma in the United States teams is an indication of a global trend at elite athletic level. Furthermore, limited data exist examining sport specific prevalence (Rundell, 2004). However, winter sports typically have a higher prevalence of asthma/EIA compared with summer sports (Rundell et al., 2000).

In 2001 the International Olympic Committee – Medical Commission (IOC-MC) changed the criteria for the use of inhaled β_2-agonists in the treatment of asthma and EIA (Appendix 1). Prior to 2001 asthmatic athletes competing at the Olympic Games required a doctor's note with signature explaining symptoms and history of asthma to enable them to use asthma medication (inhaled β_2-agonists). Since 2001 all athletes who wish to use inhaled β_2-agonists (IBAs) as therapeutic treatment of asthma in Olympic competition must submit objective evidence of asthma to justify their use (Anderson et al., 2003). An athlete is now required to submit an abbreviated therapeutic use exemption form (Appendix 2), which includes the maximum flow-volume loops from either a bronchoprovocation or bronchodilator challenge in addition to a past history of asthma, required medication and doctor's signature. This decision by the IOC-MC provided the initial stimulus to investigate exercise induced asthma (EIA) within British elite athletes.

Common symptoms associated with EIA include wheezing, coughing, excess mucus production and dyspnoea. It is common however, for many athletes not to report any symptoms of EIA, but present with EIA following bronchoprovocation challenges (Rundell et al., 2001). The IOC-MC accepts bronchodilator and bronchoprovocation challenges as objective evidence of EIA. Most athletes require a bronchoprovocation challenge as their forced expiratory volume in one second (FEV_1) is above 90% of their predicted value at rest. Despite an exercise challenge being the most specific challenge for EIA (Anderson et al., 2003; 2005), approximately half the submissions to use inhaled β_2-agonists at the Salt Lake City 2002 winter Olympic Games were direct airway challenges such as methocholine and histamine (Anderson et al., 2003). Direct airway challenges have been shown to have a lower sensitivity and specificity compared with indirect airway challenges such as exercise and eucapnic voluntary hyperpnoea (EVH) (Holzer et al., 2002). Due to the large number of challenges accepted as evidence for EIA by the IOC-MC and the variety of challenges submitted to the IOC-MC at the Salt Lake City 2002 winter Olympic Games the most appropriate challenge in the assessment of EIA in elite athletes remains unclear.

At present there is no 'gold standard' measurement of airflow for the diagnosis of EIA in athletes, or non-athletes (Godfrey, 1999). In all EIA tests recognised by the IOC-MC, FEV_1 is the parameter of choice by which changes in maximal expiratory function are assessed. Despite the absence of a 'gold standard' measure for the diagnosis of EIA in athletes, the IOC-MC has ruled that an exercise or EVH challenge is positive for EIA when the FEV_1 falls $\geq$10% from the baseline measurement. It is possible that the addition of other measurements of expiratory lung function may provide greater sensitivity and specificity in the diagnosis of EIA. For example, Forced Expiratory

Flow between 25-75% of vital capacity (FEF_{25-75}) has been used in conjunction with FEV_1 to aid the diagnosis of EIA in children (Custovic et al., 1994; Fonseca-Guedes et al., 2003) and athletes (Rundell et al., 2000). Implicitly, FEV_1 measures expiratory flow at high and mid-lung volumes, whereas FEF_{25-75} and Forced Expiratory Flow at 50% of vital capacity (FEF_{50}) are markers of expiratory flow through middle lung volumes. It has been suggested that FEF_{25-75} and FEF_{50} are more sensitive to airway obstruction in the small airways than FEV_1 (McFadden and Linden, 1972; Lebecaque et al., 1993). Custovic et al. (1994) demonstrated the combined application of FEV_1 (-10%) and FEF_{25-75} (-26%) criteria enabled detection of all subjects with EIA, with no false positive diagnosis of non-asthmatics. Thus, the Custovic et al. (1994) study provides promising evidence supporting the addition of mid-expiratory flow-rates to FEV_1 in the diagnosis of EIA in children that may be valuable in the assessment of the elite athlete.

There are a number of medications that have been reported to attenuate EIA including: inhaled corticosteroids (Adams et al., 2001a; 2001b), short and long acting inhaled β_2-Agonists (Scottish Intercollegiate Guidelines Network (SIGN), 2002), theophylines (Nassif, 1981; SIGN, 2002), leukotrienes receptor agonists (SIGN, 2002), chromes (Kelly et al., 2001) and β_2-Agonists tablets (SIGN, 2002). At present inhaled corticosteroids and inhaled β_2-Agonists are recommended as the first line treatment for individuals with asthma by the British Thoracic Society (BTS) (2004).

Since 1976 it has been accepted that inhaled β_2-agonists are effective relievers of EIA (Anderson et al., 1976). Within the elite athletic population the number of submissions for inhaled β_2-Agonists has increased at each Olympic Games since 1984 (IOC-MC, 2002). However, Anderson and Brannan (2004) have recently reported that the long-

term use of inhaled β_2-agonists may lead to a worsening of asthma severity. Anderson and Brannan (2004) argue the increase in the severity is due to the down regulation of β_2-receptors in the lung (Barnes, 1995) and the stimulation of chloride secretion and movement across the epithelial cells to the airway surface, which leads to the dehydration of the airway submucosa (Boucher, 1994). Furthermore, the use of once daily long-acting β_2-agonists results in a reduction in the duration of airway protection from bronchoconstriction (Hancox et al., 2002; Simons et al., 1997). Therefore, the individual use of β_2-Agonist therapy to attenuate EIA should be used with caution as this treatment does little to attenuate the underlying inflammatory and remodelling processes that may occur. Despite this many athletes still use inhaled β_2-agonists as their only source of therapy to attenuate EIA.

Inhaled corticosteroids have previously been reported to be associated with a reduction in inflammatory cells in the airway (Schleimer, 1983) as well as improve symptoms, lung function and exacerbation frequencies (Dompeling et al., 1993). Therefore, the use of inhaled corticosteroids should attenuate the potential airway remodelling processes that may occur within EIA individuals. Despite this, recent studies have reported that the addition of long-acting inhaled β_2-Agonists to corticosteroid therapy leads to better control of symptoms and lower frequency of asthma exacerbations (Shrewsbury et al., 2000; Koopmans et al., 2005; Masoli et al., 2005). However, Aziz et al. (2000) reported that patients preferred the combination therapy but that it provided no greater effect on the inflammatory markers, exhaled nitric oxide and serum eosinophilic cationic protein, than corticosteroid therapy alone.

As there is currently no cure for asthma/EIA it is important once an athlete presents EIA, following a recognised IOC-MC test, they receive optimal pharmaceutical treatment, which will lead to improvements in well being and performance. However, there are few controlled studies that have been conducted on the effects of anti-asthma drugs and elite athletes (Helenius et al., 2005).

1.1 Aims

The aims of this PhD are to investigate:

1) The prevalence of EIA within the British Olympic Team at the 2000 Sydney Olympic Games and 2004 Athens Olympic Games with special reference to the introduction of the IOC-MC asthma guidelines

2) The impact of mid-expiratory measures of airflow on the sensitivity and specificity of EIA diagnosis

3) The diagnosis of EIA in elite athletes through EVH and exercise challenges

4) The optimal pharmaceutical therapy for elite athletes with EIA.

Chapter 2

Literature Review

Asthma obstructs expiratory airflow in susceptible individuals. The airflow obstruction is a result of smooth muscle contraction, inflammation and remodelling in the upper and lower airways that can be reversed and controlled with suitable treatment. Asthma can manifest itself in a variety of ways and symptoms include wheezing, coughing and breathlessness. These symptoms can vary between individuals, especially when individuals are exposed to triggers such as cold air, exercise, viral upper airway respiratory infection, cigarette smoke, pollution, and respiratory allergens. This literature review will discuss the prevalence and basic pathophysiology of asthma leading to a discussion of exercise induced asthma (EIA) and the implications that it may have for elite athletes.

2.1 Prevalence of Asthma

Asthma has only become a public health issue since the 1960s. Since this time, surveys suggest that the prevalence of asthma is increasing. For example, between 1978 and 1988 asthma prevalence within school children living in Wales increased 5% (Burr et al., 1989) and in Scotland the chance of children developing lifetime asthma increased from 10% in 1989 to 20% in 1994 (Omran and Russel, 1996). These data demonstrate that asthma prevalence is increasing in children within the UK and are commensurate with data on the global prevalence of asthma in children (Magnus and Jaakkola, 1997; Nysted et al., 1998; Downs et al., 2001). Increases in adult asthma seem to be occurring at similar rates to increases in childhood asthma (Hansen et al., 2000; Peat et al., 1992). Brogger et al. (2003) reported that the risk of asthma in adults living in Norway, aged

less than 40 years, had tripled between 1972 and 1999. Asthma prevalence over this period increased from 3.6% to 7.6% in males and from 3.2% to 10.7% in females.

Asthma prevalence has been shown to be significantly different between sexes. In childhood, boys have a higher prevalence of asthma than girls (Kao et al., 2001; Joseph et al., 1998; Schaubei et al., 1996; Skobeloff et al., 1991; To et al., 1996; Wilkins and Mao, 1993; Hyndman et al., 1994; Bloomberg et al., 2003) however, women above the age of 22 years have a higher asthma prevalence than men of similar ages (Cydulka et al., 2001; Krishman et al., 2001; Prescott et al., 1997; Singh et al., 1999; Awadh et al., 1996; Tuuponen, 1993; Legoretta et al., 1998; Trawick., et al 2001). Most recently, Schatz and Carmargo (2003) studied 60,694 asthmatics living in Southern California. They reported between the ages of 2-13 a greater number of males (63%) had been diagnosed with asthma compared with females (37%) of the same age. Furthermore, the severity of asthma was greater in males. This trend was reversed (males 35% and females 65%) for those aged between 23-64 years, with asthma severity also being greater in females compared with males of the same age. The potential mechanisms for these trends are not clearly understood; however, it has been suggested that sex hormones (Hermano et al., 1998; Kirsch et al., 1999), changes in airway size (Britton et al., 1994), anxiety-depression (Von Brehan et al., 2002) or obesity (Carmargo et al., 1999; Guerra et al., 2002) may contribute to the observed changes in asthma prevalence and severity in males and females across the lifespan.

Current research suggests that asthma prevalence is rising across all age groups. The mechanisms underlying this increase are not clearly understood; however, a number of potential mediators have been suggested. Increased exposure to environmental factors,

such as pollution, may increase the risk of an individual developing asthma. Flodin and Jonsson (2004) reported that three or more years working in polluted environments was associated with an increased risk of developing asthma and exposure to pollution caused by road traffic has also been linked to a greater risk of asthma development in children (Zmirou et al., 2004). It has been documented that children who live in areas with high ozone concentrations and who exercise frequently have a higher risk of developing asthma than children who are similarly active but live in areas with low ozone concentrations (McConnell et al., 2002). McConnell et al. (2002) recorded the incidence of asthma over the period 1993-1998 in 3,535 children who lived in either a low ozone area (37.7-67.9 ppb) or a high ozone area (69.3-87.2 ppb). The activity levels of the children were quantified by the number of sports they participated in (1, 2, 3+). The overall risk of developing asthma was not greater for children living in high ozone areas compared to the children living in low ozone areas; however, those who played 3+ sports in a high ozone area were at a greater risk of developing asthma than those who played 3+ sports in a low polluted area. This study suggests that high physical activity levels in high ozone areas leads to a greater risk of the development of asthma. Increases in exposure to pollution may be one reason why asthma prevalence has increased in developed countries; however, other factors that may have contributed to this are increased prosperity, increased awareness of asthma and easier access to doctors (Pearce, 1998). Whilst the mechanisms underlying the increased asthma prevalence are not fully understood it is clear that insights into the pathophysiology, optimal diagnosis and treatment of asthma will help reduce the impact of asthma in susceptible individuals.

2.2 Pathophysiology of Asthma

In the airways of a non-asthmatic, the smooth muscle surrounding the bronchioles and bronchi are relaxed and the bronchial epithelium is not inflamed, which allows non-asthmatics to inhale and exhale air with relative ease when at rest or exercising. During an asthma 'attack' the airways display inflammation, smooth muscle contraction, and mucosal gland hyper-secretion (Fireman, 2003). At microscopic levels the following events occur within the larger and smaller airways, leading to decreased baseline airway calibre and exaggerated airway narrowing in susceptible individuals:

- Hyperplasia of the smooth muscles of the bronchus and bronchioles
- Thickening of the submucosal basement membranes
- Mucosal oedema throughout the lung tissue
- Sloughing of the mucosal epithelium
- Loss of ciliated epithelium cells
- Mucous gland hypertrophy in the submucosa

The decreased baseline airway calibre and exaggerated airway narrowing result in restricted expiratory airflow that is typified by a reduced Forced Expiratory Volume in one second (FEV_1) (figure 2.1). In a 15-year follow-up study, Lange et al. (1998) conducted measurements of FEV_1 in asthmatics and non-asthmatics (figure 2.2). The study was conducted between 1976 and 1994 and included 17,506 subjects of whom 1,095 had asthma. Among women and men, and among smokers and non-smokers, the decline in FEV_1 over time was greater in subjects with asthma. The average drop in FEV_1 for a non-asthmatic was 22 ml per year, and 38ml per year for an asthmatic. It is normal to expect a reduction in lung function over time (years) in non-asthmatics, but the reduction in lung function seems to be accelerated in individuals with asthma.

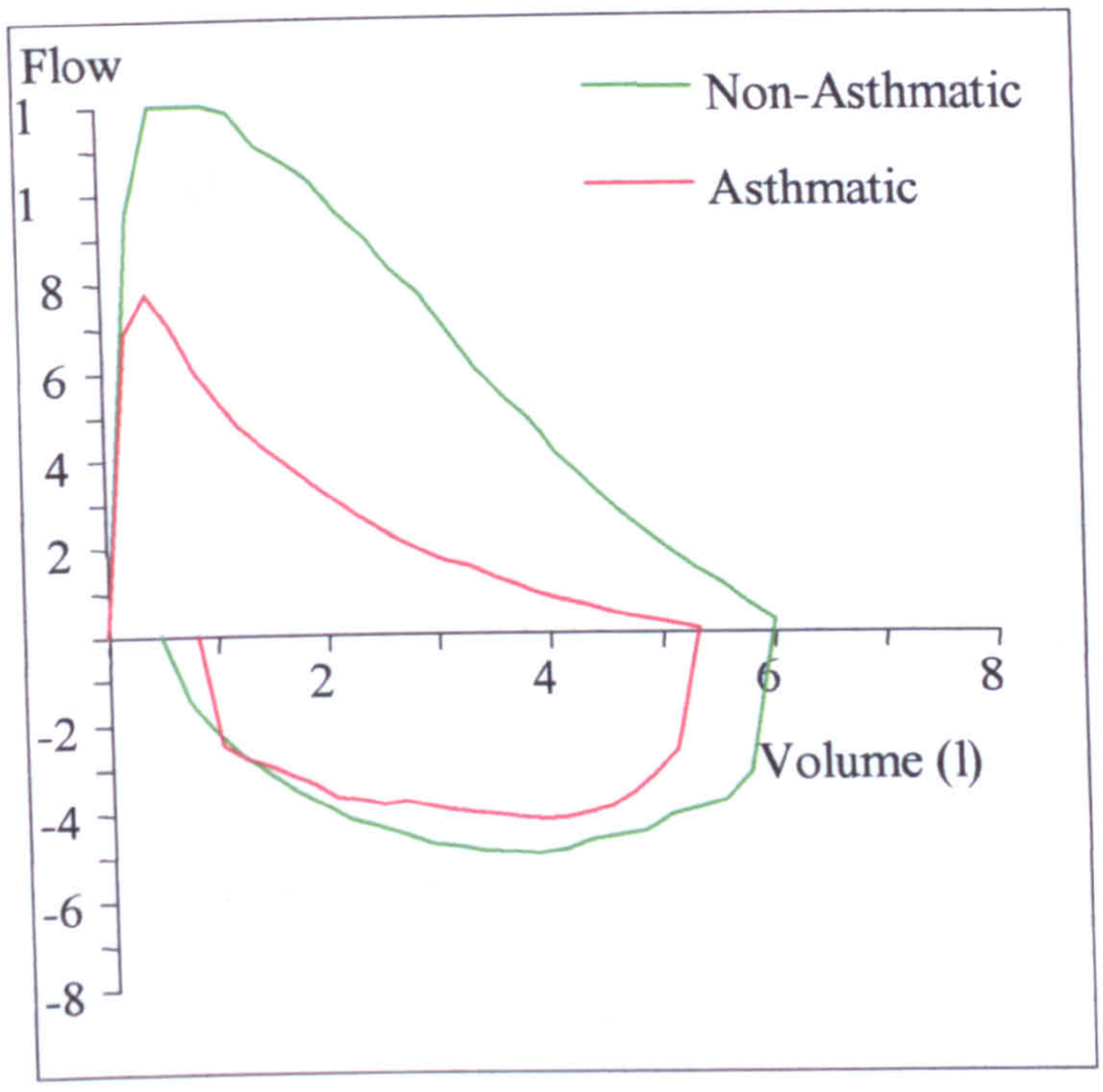

Figure 2.1: Maximal Voluntary Flow Volume Loop: Asthmatic vs Non-Asthmatic.

The maximal flow volume loops illustrate the difference in the level of obstruction within the airway between a non-asthmatic and an asthmatic of similar height, weight, age and ethnicity. The reduced PEF rate and subsequent scalloping during expiration results in the asthmatic presenting with a lower FEV_1 compared with the non-asthmatic.

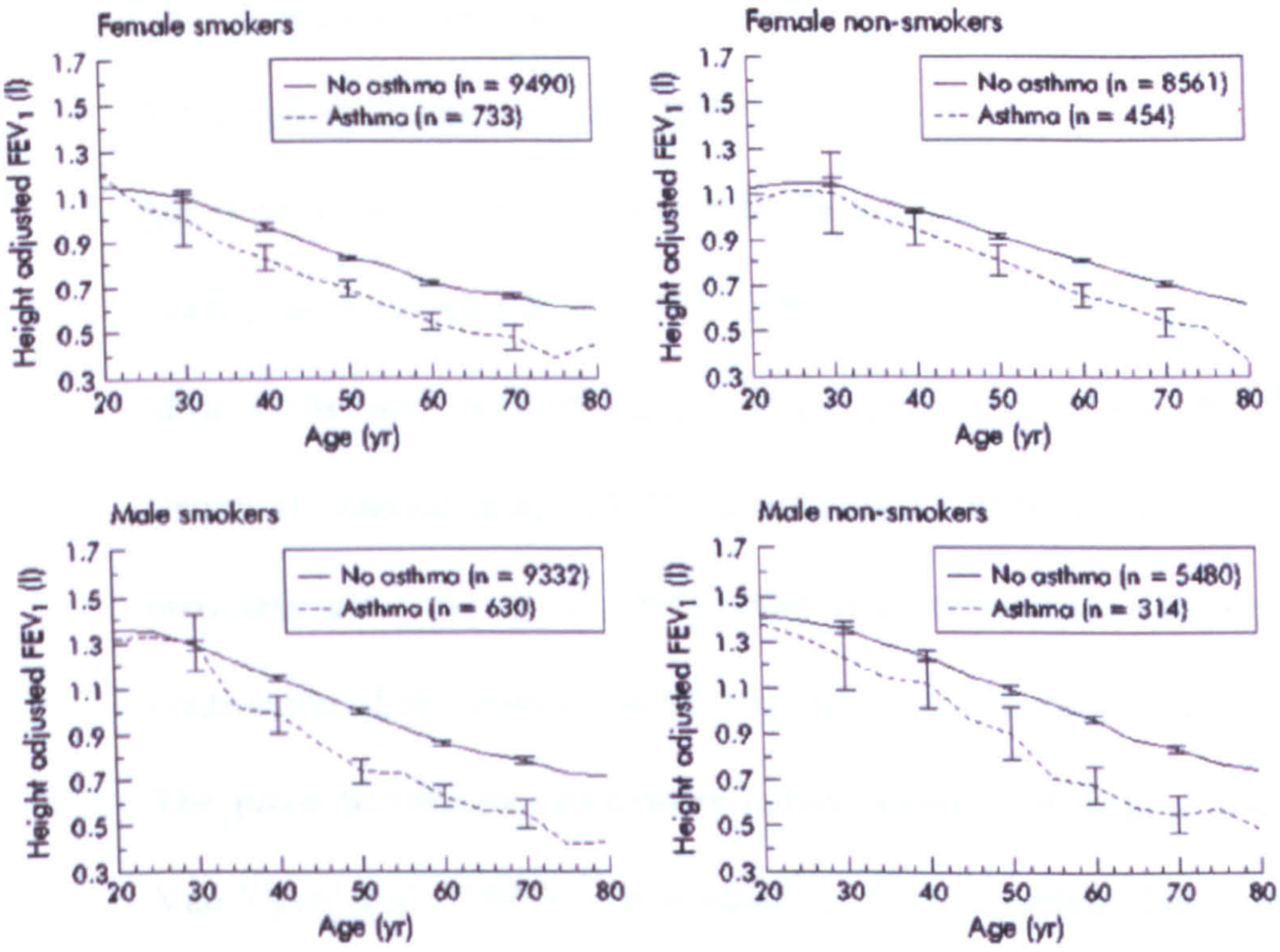

Figure 2.2: Changes of lung function with age (*from Lange, P., Parner, J., Vestibo, J., Schnohr, P. & Jensen, G. (1998). A 15 year follow up study of ventilatory function in adults with asthma. New England Journal of Medicine, vol. 339, pp. 1194-1200*).

Inflammation

Airway inflammation is a major cause of airway calibre reduction and is thought to be produced by two different mechanisms (Bousquet et al., 2000). The first of these mechanisms is allergic inflammation, which is characterised by elevated levels of immoglobulin E (IgE) that is associated with TH2-lymphocyte response. The second mechanism involves pro-inflammatory cytokines, enzymes and growth factors generated by the damaged bronchial epithelium and submucosal cells of the activated airway that leads to structural changes of the bronchial tissues (airway remodelling). The allergic inflammatory response is thought to be a characteristic of acute inflammation and may be caused by several known or unknown factors such as allergens (Platts-Mills and Wheatley, 1996), viruses (Busse and Gern, 1997), or pollutants (Wardlaw, 1993). Inflammation may also be caused by exercise hyperpnoea or hyperventilation. Bousquet et al. (2000) outlined the series of events that are thought to occur during acute inflammation:

- Activation of allergen specific IgE
- Rapid activation of airway mast cells (Murray et al., 1985; Liu et al., 1991) and macrophages (Tonnel et al., 1983; Calhoun et al., 1992)
- Mast Cells and Macrophages release proinflammatory mediators such as histamine (Jarjour et al., 1997), eicosanoids (Wenzel et al., 1989), leukotrienes, prostaglandin (Cho et al., 2002) and reactive oxygen species, which induce contraction of the airway smooth muscle, mucus secretion and vasodilatation
- The pro-inflammatory mediators induce vascular leakage (Grieff et al., 1993; Van-Vyve et al., 1995), which contains plasma protein that induce a thickened engorged and edematous airway wall
- The combined result is a narrowing of the airway lumen.

The acute inflammation is known as the early phase-reaction and can be followed by a late phase inflammation. The late phase inflammation typically occurs 6-9 hours following the initial acute inflammation and involves the recruitment of eosinophils (De Monchy et al., 1985), $CD4^+$ T cells (Robinson et al., 1993), basophils (Guo et al., 1994), neutrophils (Koh et al., 1993; Montefort et al., 1994) and macrophages (Calhoun et al., 1993). The late phase is characterised by the selective retention of T cells (Gratziou et al., 1996), the expression of adhesion molecules (Lassalle et al., 1993; Georas et al., 1992) and release of pro-inflammatory mediators (Liu et al., 1991; Smith et al., 1992). This late phase inflammation reaction has been used as a model system to study the mechanisms of chronic inflammation (Holgate, 1993; Bochner et al., 1994).

The susceptibility of an individual to either an acute or chronic inflammation depends on the number of inflammatory cells lining the airways. As previously discussed airway inflammatory cells exist within the healthy airway, but their number is controlled by apoptosis. Apoptosis terminates the inflammatory process by reducing the number of inflammatory cells within the airway. The two principal cytokines that promote mast cell proliferation and differentiation are Interleukin-3 (IL-3) and stem cell factor (SCF) (Cho et al., 2002). IL-3 appears to be important for proliferation, whereas SCF maintains mast cell viability and promotes maturation (Bianchine et al., 1992; Blechman et al., 1993). Fibroblasts produce SCF when they are activated by allergic inflammation. When the levels of SCF are increased the survival rate of mast cells would also increase due to a reduction of apoptosis (Cho et al., 2002) and increased adhesion expression of adhesion molecules to epithelial cells (Vignola et al., 1993; Canonica and Ciprandi, 1994). Other pro-inflammatory cells such as eosinophils are thought to increase due to a reduction in apoptosis (Wooley et al., 1996; Sousa et al.,

1993). Therefore, if apoptosis is reduced there is potential for acute inflammation to develop into chronic inflammation. One benefit of using treatments such as glucocorticoids is that they increase the rate of apoptosis and therefore reduce the inflammatory response. For example, glucocorticoids such as fluticasone proprionate reduce the survival of pro-inflammatory cells such as eosinophils and mast cells (Anderson,1996; Her et al., 1991; Wallen et al., 1991; Meagher et al., 1996; Adachi et al., 1996; Mentz et al., 1995).

Bronchial Epithelium

The bronchial epithelium is in a key position where gene-environment and environment-environment interactions can occur. The bronchial epithelium acts as a barrier between the internal environment of the body and the external environment, and it is continuously exposed to gaseous and particulate components of the external environment. Thus, the epithelium is involved in many of the reactions that lead to airway inflammation and smooth muscle contraction.

When exposed to inhaled pollutants, infectious agents and other particulate matter, the epithelium acts as a protective barrier. When the epithelium is exposed to these irritants it releases pro-inflammatory mediators that help to protect the internal milieu of the lungs. Salvi et al. (2000) demonstrated that diesel exhaust particles cause epithelial activation with increased expression of interleukin-8 (IL-8), which was consistent with the observed increase in neutrophils in bronchial biopsies and lavage fluid following exposure. Similar reactions from the epithelium have been demonstrated when exposed to dust mite proteolytic allergens (King et al., 1998) and following rhinovirus infection (Papadopoulos et al., 2000). A healthy bronchial epithelium is able to repair itself

rapidly, which enables the down regulation of the inflammatory response caused by acute exposure to potential asthma triggers. When an asthmatic bronchial epithelium is exposed to potential asthma triggers it has an increased susceptibility to inflammation due to an increase in the production of remodelling growth factors and mucus production as well as an inability to repair rapidly (Holgate, 2002). This inadequate repair response and epithelial damage may lead to heightened airways responsiveness (Jeffery et al., 1989; Ohashi et al., 1992), a failure to metabolise agonists (Inoue et al., 1992), the destruction of the diffusion barrier altering permeability of airway mucosa (Sparrow and Mitchell, 1991), the depletion of epithelial-derived relaxant factors (Rabe et al., 1995) and loss of enzymes responsible for degrading pro-inflammatory neuropetides (Lilly et al., 1993) (figures 2.3, 2.4 and 2.5). The implications of this being an increase in asthma symptoms, exacerbation frequency and severity.

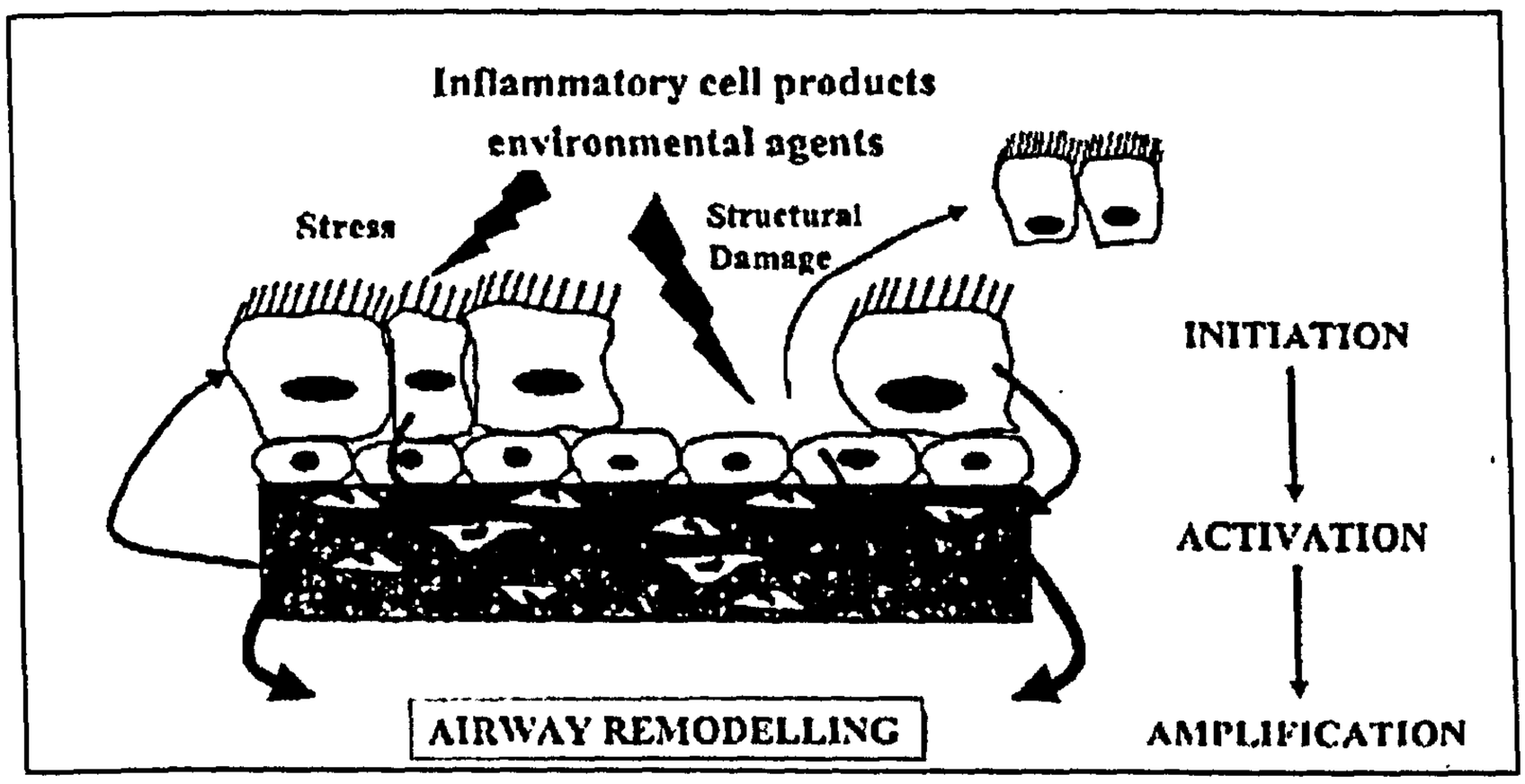

Figure 2.3: Sloughing of the asthmatic bronchial epithelium caused by inhaled environmental agents *(From: Fireman, P. (2003). 'Understanding Asthma Pathophysiology'. Allergy and Asthma Proceedings, vol. 24, pp. 79-83)*

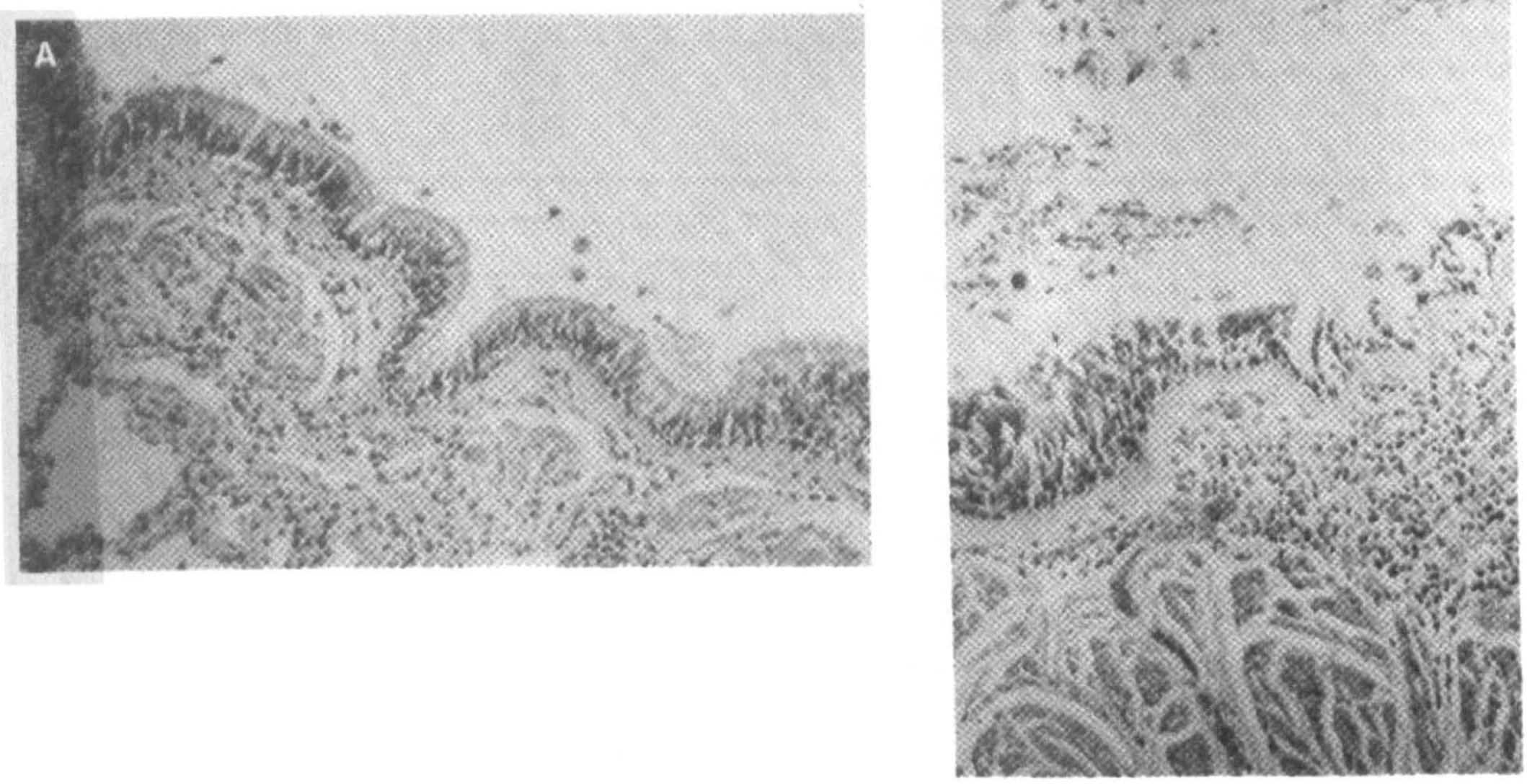

Figure 2.4: Bronchial Epithelium of a normal and asthmatic subject

Panel A of Figure 2.4 is a normal bronchial epithelium from a subject who died accidentally. Show epithelium is intact, few numbers of inflammatory cells and bronchial smooth muscle. Panel B of Figure 2.4 is a bronchial epithelium of a subject who suffered from fatal asthma. Shows epithelial sloughing, thickened reticular basement membrane, intense infiltration of the mucosal by inflammatory cells and enlargement of the bronchial smooth muscle. *(From: Bousquet, J. Jeffery, P. Busse, W. Johnson, M. & Vignola, A. (2000). 'From Bronchoconstriction to Airways Inflammation and remodelling'. American Journal of Respiratory and Critical Care Medicine, vol. 161, pp. 1720-1745)*

Airway Remodelling

Acute inflammation generally leads to repair and restoration of normal structure and function to the airway. Chronic inflammation may result in an altered structure (Rennard, 1996) such that airway remodelling occurs. This involves epithelial shedding, sub-basement thickening, smooth muscle hyperplasia and an increase in the number of nerves and blood vessels. These changes result in increased resistance to airflow particularly when there is bronchial contraction and bronchial hyperresponsiveness (Boulet et al., 1995; Kamn and Drazen, 1992). Airway muscle mass may increase in volume by 3-4 fold in an asthmatic (Hogg, 1993). This increase has been found in major

bronchi (Dunnil et al., 1969) and in peripheral airways (Saetta et al., 1991; Carroll et al., 1993) with muscle mass being thickest in the major bronchi.

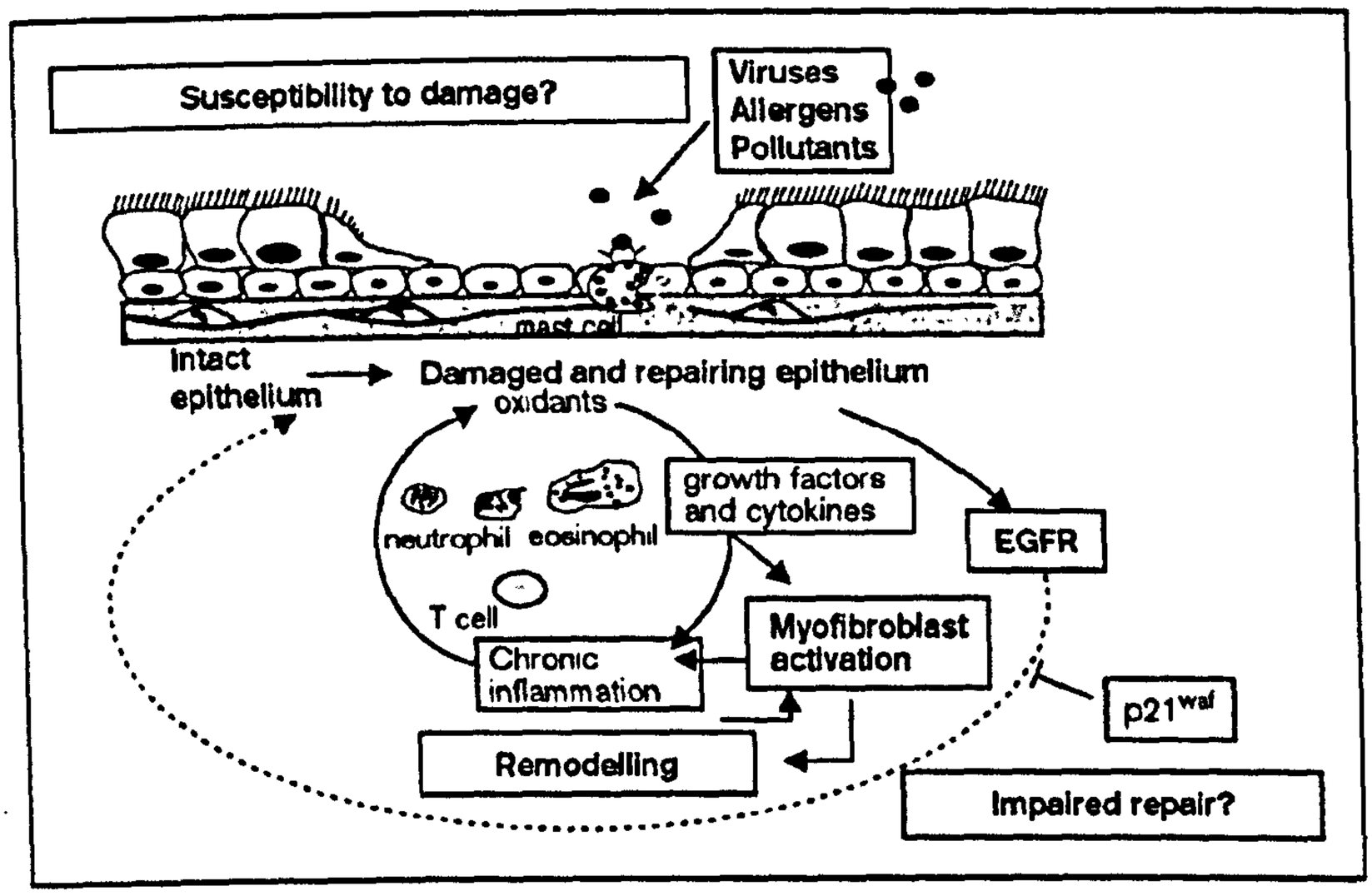

Figure 2.5: Epithelial injury, airway inflammation and remodelling *(From Davies, D. (2001). 'The bronchial epithelium: translating gene and environment interactions in asthma'. Current Opinion in Allergy and Clinical Immunology, vol. 1, pp. 67-71)*

The thickening of the reticular basement membrane is a typical characteristic that occurs early on in the asthmatic bronchus (Dunnill et al., 1969). This thickening is usually homogenous and hyaline in appearance. In asthma the basal lamina is of normal thickness whereas the reticular layer is thickened, which is associated with deposition of immunoglobins, collagen I and III, and fibronectin (Altraja et al., 1996). The degree of thickening has been related to the severity of asthma (Chetta et al., 1997); however it is generally thought to have no significant correlation with the severity of asthma (Jeffery et al., 1989; Saetta et al., 1996). Another feature of airway remodelling is an increase in the number of blood vessels surrounding the airways. These new vessels originate by budding or sprouting of pre-existing vessels by angiogenesis (Battegay, 1995). The new blood vessels have been found to be hyperpermeable and increase oedema. During

airway remodelling, concomitant to an increase the number of blood vessels is an increase in vessel area (Saetta et al., 1991; Carroll et al., 1993). Thus, asthmatics have a greater number and size of vessels than non-asthmatics in their airways (Li and Wilson, 1997). The increase in muscle mass, reticular basement membrane and number and size of vessels in the asthmatic airways, results in a thickened airway wall that contributes to airway remodelling and a reduction in expiratory airflow in asthma (due to incursion into the airway lumen).

In summary, the prevalence of asthma has been increasing within the general population since the 1960's. Triggers for asthma include exercise, dust, pollution and pollen. Exposure to these triggers can lead to susceptible individuals presenting with inflammation, smooth muscle contraction and mucosal gland hyper-secretion within the small airways, which limit expiratory airflow leading to reduced measures of expiratory function such as FEV_1. The inflammatory mediators that are released from mast cells and macrophages during an acute asthmatic episode include cytokines, prostaglandins, leukotrienes, histamine and eicosanoids. Prolonged exposure to these inflammatory mediators can lead to an increased mast cell survival rate and a reduction in apoptosis within the airways, which may lead to the development of chronic inflammation. Chronic inflammation can result in airway remodelling that leads to a reduction in expiratory airflow and potentially to the development of chronic asthma. It is therefore important that individuals who suffer from acute episodes of asthma receive correct diagnosis and suitable therapy to prevent the potential airway remodelling and increases in severity.

2.3 Exercise Induced Asthma (EIA)

The first record of exercise induced asthma (EIA) was reported approximately 1,800 years ago by Aretaeus (120-200AD) who noted that physical exertion provoked airway obstruction (Adams, 1856). EIA is currently defined as a transient narrowing of the airways following exercise and is present in approximately 80-90% of people with asthma (Anderson, 1997). EIA is associated with smooth muscle contraction, airway inflammation and mucus production developing maximally approximately five to ten minutes after cessation of exercise (Rundell et al., 2000). EIA is characterised by a broad spectrum of symptoms similar to those observed in asthma. In individuals with a mild to moderate asthma severity, exercise may be the sole trigger in the genesis of bronchoconstriction. Therefore, exercise has the potential to be a valuable tool when the diagnosis of asthma is in doubt. In the literature, EIA has also been termed exercise induced bronchoconstriction (EIB), however within this literature review the term EIA will be employed as the two terms describe the same processes.

2.4 Prevalence of EIA

The prevalence of EIA in athletes is higher than the 8% asthma prevalence rate of general population of the UK (Asthma UK, 2001; Helenius et al., 1998; Wilber et al., 2000). The prevalence of asthma/EIA in athletic populations has steadily increased (see table 2.1) since Voy (1986) first reported the prevalence of asthma in the 1984 United States Olympic team as 11%. Since 1984 the prevalence within the United States Olympic team has been reported at 14% in 1996 (Weiler et al., 1998) and 17% at the 1998 Winter Olympics (Weiler and Ryan, 2000). Athletes who compete in winter sports have a higher prevalence of EIA than those who compete in summer sports (Rundell et al., 2000), which suggests the environment that an individual trains and competes in

may be an important precursor in the development of EIA. For example, the 1996 U.S. Summer Olympic Team had a prevalence of 14%, whereas winter sports such as ice-skating had a reported prevalence of 30 – 35% (Craig et al., 1996; Mannix et al., 1996). Wilber et al. (2000) have also reported high prevalence rates in winter athletes such as cross-country

Author	Prevalence	Population	Method of diagnosis
Voy, 1986	11%	U. S. Olympic Athletes	Symptom and family history
Mannix et al., 1996	35%	Figure Skaters	Exercise Challenge FEV_1 >15%
Helenius et al., 1996	25%	Elite runners	Exercise Challenge FEV_1 >4.7 (2 SD)
Schoene et al., 1997	15%	Elite track and field	PEF >10%
Kukafka et al.,1998	20%	American Football	Exercise Challenge PEF >10%
Helenius et al., 1998	26%	Elite runners	Exercise challenge FEV_1 >6.5% = 2 SD
Weiler et al., 1998	14%	U. S. Olympic Squad	Survey
Mannix et al., 1999	55%	Figure Skaters	Exercise and EVH challenge FEV_1 >10%
Weiler and Ryan, 2000	17%	U. S. Olympic Winter Athletes	Athlete questionnaire
Wilber et al., 2000	23%	U.S. Olympic Athletes	Exercise Challenge FEV_1 >10%
Nystead et al., 2000	Elite athletes 10%, General Population 7%	Athletes and non-athletes	Survey
Rundell et al., 2001	Exercise challenge 26%, Questionnaire 29%	Elite Athletes	Exercise challenge FEV_1 >10% and Questionnaire
Thole et al., 2001	14%	Collage Athletes	PEF >15%
Ogston and Butcher, 2002	28%	Cross country skiers	Exercise Challenge FEV_1>10%
Hallstrand et al., 2002	9%	High School athletes	Exercise challenge FEV_1 >10%
Mannix et al., 2003	19%	Gym users	EVH either FEV_1 >10%, FEF50 > 20%, PEF >25%
Kippelen et al., 2004	4%	Endurance athletes	Questionnaire
Rundel et al., 2004	Exercise challenge 29%, EVH 45%	Elite Winter athletes	Exercise and EVH challenge FEV_1 >10%
Alaranta et al., 2004	Athletes 13.9% Control 8.4%	Finnish Olympic Athletes	Questionnaire

Table 2.1: Prevalence of EIA in athletic populations

skiers, where 50% [(females (57%) vs males (43%)] were diagnosed with EIA. The Wilber et al. (2000) study also demonstrated that the overall prevalence of EIA was higher in females (23%) than males (18%) and this overall trend was consistent through all of the seven winter sports examined. What remains unclear is whether the observed increase in the prevalence of EIA in the United States teams is an indication of a global trend within elite athletes. Further, limited data exists examining sport specific prevalence across both winter and summer sports.

2.5 Pathophysiology of EIA

During normal resting conditions, the nasal airway is involved in conditioning the inhaled air resulting in an alveoli air temperature of 37°C that is fully saturated with water (Hahn et al., 1984). During exercise, minute ventilation ($\dot{V}_E$) is greatly increased and breathing through the mouth predominates over nasal breathing. This increase in breathing through the mouth causes inhaled air to bypass the nasal warming and humidifying process. The lower airways, therefore, become exposed to 'unconditioned' air that will not only require warming and humidifying but, may also contain particles such as pollution, dust or pollen. As individuals exercise to higher intensities, their $\dot{V}_E$ continues to increases leading to larger doses of 'unconditioned air' reaching the lower airways. The exact mechanisms that lead to expiratory flow limitation (through inflammation and smooth muscle contraction) following exercise are unclear. However, it has been proposed that EIA may occur through several mechanisms, but two main hypothesis predominate; 1) osmotic, 2) thermal hypothesis.

Thermal Hypothesis

The thermal hypothesis suggests EIA is initiated through airway cooling during exercise that is followed by a rapid warming of the airways following cessation of exercise (Deal et al., 1979). The rapid rewarming of airways is thought to produce vasodilatation of the pulmonary capillaries causing bronchial congestion (McFadden et al., 1986; McFadden, 1987). This hypothesis therefore, suggests that airway narrowing is a direct consequence of these events. Anderson and Daviskas (2000) have highlighted that the thermal hypothesis does not accommodate smooth muscle contraction or inflammatory markers. Furthermore, the thermal hypothesis fails to account for the fact that EIA can occur in dry air, which can be either hot or cold (Deal et al., 1979; Evans et al., 2005). Hahn et al. (1984) and Deal et al. (1979) have both reported that FEV_1 following exercise did not alter when the water loss form the airway remained the same but, the temperature was altered. Water loss in these studies was calculated by assuming full saturation of the expired air at the temperature measured, which was later questioned by Eschenbacher and Sheppard (1985). Using a more reliable measure of water loss Eschenbacher and Sheppard (1985) demonstrated that heat loss was not the sole trigger for EIA and respiratory water loss was also important. Eschenbacher and Sheppard (1985) measured water loss by separating the inspired and expired air and measured both humidity and temperature during hyperventilation with cold air. Other studies also failed to provide strong support for the thermal hypothesis (Ingenito et al., 1988; Argyros et al., 1993; Evans et al., 2005), and suggest that water loss is essential for the development of EIA.

Osmotic hypothesis

Due to the failure of the thermal hypothesis to account for established findings regarding the pathogenesis of EIA, the osmotic hypothesis of EIA was developed as a possible explanation. The osmotic hypothesis suggests that the dehydration and the osmotic effects of water loss (caused by the increased volume of 'unconditioned' air entering the airway during exercise) initiates events leading to EIA (Anderson, 1984). The osmotic changes occur in the airway surface liquid (Anderson, 1984) and epithelial cells (Anderson et al., 1989), due to the respiratory water loss, which also leads to submucosal involvement signalling bronchial blood flow (Anderson and Daviskas, 1992). The hypothesis is based around the understanding that an increase in osmolarity produces a favourable environment for mediators to be released, which causes the smooth muscle to contract, limiting expiratory air flow. Other cells such as mast cells, eosinophils, macrophages and sensory nerve cells can potentially be subjected to cell volume loss (figure 2.6). This can lead to further inflammatory mediator release, which is stimulated by the regulatory volume increase, after cell shrinkage (Anderson and Daviskas, 2000). Experimental support for the osmotic theory has been provided by Strauss et al. (1978) and Anderson et al. (1982). They reported the severity of EIA is directly proportional to the water content of inspired air and the water loss at the mouth. In addition, they noted that when water loss was prevented, so too was EIA, even in severe asthmatics. As EIA can occur without significant cooling, the osmotic effects are thought to be more important than the thermal effects (Anderson and Daviskas, 1993; Evans et al., 2005). Airway cooling and rapid rewarming do occur, however, they are not prerequisites for EIA. The osmotic hypothesis appears to accommodate the established pathophysiology of EIA and asthma.

Additional Triggers

As previously discussed exercise results in an increase in 'unconditioned' air inspired through the mouth due to an increased $\dot{V}_E$ during exercise, which results in bronchoconstriction in susceptible individuals. However, the EIA response (especially in atopic individuals) may be more complex. For example, an individual who does not have an EIA response under normal exercise conditions may respond if exercise is accompanied by another asthma trigger such as pollution or pollen. Therefore the pathophysiology leading to bronchoconstriction in susceptible atopic individuals may involve changes in airway osmolarity due to large volumes of 'unconditioned' air, including greater concentrations of triggers such as pollen, entering the airways. Helenius et al. (1998) demonstrated that EIA severity is related to allergen response; the more 'allergic' asthmatics are, the more severe their EIA. Helenius et al. (1998) compared falls in FEV_1 after an exercise challenge between those who suffered from EIA in the winter and those who suffered in the pollen season. The results demonstrated that more athletes demonstrated a fall in FEV_1 post exercise in the cold, but those who demonstrated falls in FEV_1 during the pollen season had larger post exercise changes. This study demonstrates that the 'pure' EIA response to cold dry air may be milder than the response to a combined trigger of exercise and pollen in affected individuals, where expiratory obstruction is more severe.

Swimming training has been shown to have a beneficial effect on the aerobic capacity of asthmatics (Matsumoto et al., 1999). Swimming can benefit those with EIA as it is generally thought that breathing the warm humid air environment reduces incidence of EIA (Bar-Or and Inbar, 1992). However, the issue of possible irritant exposure resulting from water chlorination have not been widely addressed. Anecdotal evidence

suggests that asthmatic individuals present with greater severity when exposed to the environment of a chlorinated pool (Mustchin and Pickering, 1979; Penny, 1983). It has also been reported that competitive swimming has a higher prevalence of asthma than other sports (Zwick et al., 1990; Helenius et al., 1998). The reasons for these observations are unknown and further studies should investigate whether irritants from water chlorination, or asthmatics choosing swimming as a sport due its protective effects against EIA, are responsible for the high EIA prevalence in swimming.

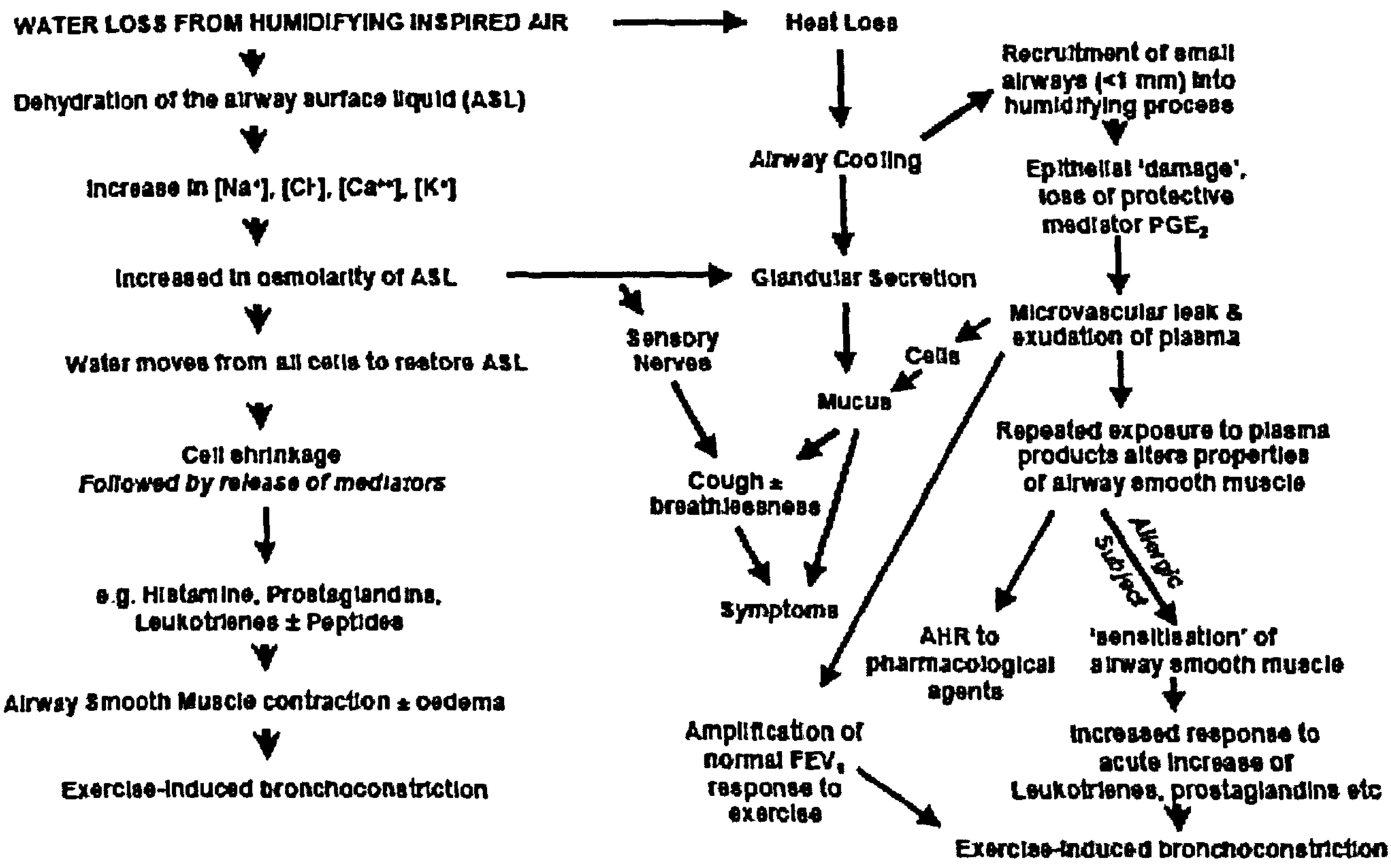

Figure 2.6: Flow-diagram of the pathogenesis of EIA

Flow chart describing the events leading to EIA in the classic asthmatic (left) and the events leading to the development of EIA in the athlete (right) *(From Anderson, S. and Kippelen, P. 2005. 'Exercise Induced Bronchoconstriction-Pathogenesis'. Current Asthma and Allergy Reports, vol. 5, pp. 116-122)*

Refractory Period

It has been reported that exercise conducted within 4 hours of an initial airway bronchoconstriction will result in bronchoconstriction that is less severe than the initial

bronchoconstriction (Argyros et al., 1995; Zach and Polgar, 1987; Malo, 1986; Rundell et al., 2003). This phenomenon is known as the refractory period and is thought to be due to a release of bronchodilating prostaglandins following the initial bronchoconstriction (Manning et al., 1993; Margolskee et al., 1988; O'Bryne and Jones, 1986; Wilson et al., 1994). Reports suggest that the refractory period does exist, however there is debate as to whether it is present within all EIA individuals (Argyros et al., 1995; Zach and Polgar, 1987; Malo, 1986; Rundell et al., 2003). Argyros et al. (1995) reported that all individuals with EIA demonstrated some level of refractory period. Argyros et al. (1995) demonstrated that the fall in FEV_1 was smaller following a second eucapnic voluntary hyperpnoea (EVH) challenge that was conducted approximately 1 hour after an initial EVH challenge, however, all 11 participants had falls in FEV_1 of $\geq$10% in the second EVH challenge. Furthermore, 3 participants had a FEV_1 fall within 5% of their initial EVH challenge. In contrast Rundell et al. (2003) reported that only 1 out of 9 winter athletes with EIA demonstrated a significant refractoriness following a subsequent sport specific exercise challenge. Studies investigating the refractory period suggest that it does not provide full attenuation to EIA and that it is not present in all athletes. Therefore the potential protective effects that are associated with the refractory period should not be relied upon by EIA athletes and should certainly not be used as an alternative for therapeutic pharmaceutical intervention.

Inspiratory Stridor

Inspiratory Stridor (IS) is a condition that is characterised by high-pitched inspiratory noise that is often mistaken for the wheeze of asthma (Brugman and Simons, 1998; Corren and Newman, 1992; Niven et al., 1992; Heiser et al., 1990; Baughman and

Loudon, 1989; Kivity et al., 1986; Lakin et al., 1984; Christopher et al., 1983). The presence of IS is associated with vocal cord dysfunction (Brugman and Simons, 1998; Corren and Newman, 1992; Niven et al., 1992; Heiser et al., 1990; Baughman and Loudon, 1989; Lakin et al., 1984) that can be diagnosed by laryngoscopy. The problem with laryngoscopy however, 1) it is very invasive, 2) the patient must be symptomatic, which is problematic if the IS is caused by high intensity exercise, thus, symptom based diagnosis is a more common and practical method.

The prevalence of IS is relatively unknown, but it has been estimated at 2-3% of the general population with the majority of cases reported in adolescent females (Sullivan, et al., 2001; Kenn and Schmitz, 1997). The prevalence within elite athletic populations has been reported to be 5%; with 53% of IS suffers also presenting with EIA (Rundell and Spiering, 2003). Rundell and Spiering (2003) also reported that it is common for IS to be mis-diagnosed as EIA, reporting 7 out of 19 athletes who were diagnosed with IS had a previous diagnosis of EIA and were prescribed β_2-agonists. It is therefore important to recognise the differences between EIA and IS before a diagnosis of either condition is made (see table 2.2).

EIA	**Inspiratory Stridor**
Occurs 5-10 minutes after exercise	Occurs during exercise and resolves within 5 minutes of stopping exercise
Wheeze on expiration	Wheeze in inspiration
Fall in FEV_1 post exercise	No fall in FEV_1 post exercise
Sound is primarily from the chest	Sound originates in the neck
EIA responds to inhaled β_2-agonists treatment	No response to inhaled β_2-agonists treatment

Table 2.2: Characteristics of EIA and Inspiratory Stridor

2.6 Diagnosis of EIA

At present, there is no gold standard methodology to diagnose EIA in elite athletes (Rundell and Jenkinson, 2002). Methods that have been used in the past include: questionnaire (symptoms based or history of medical diagnosis), exercise challenge, eucapnic voluntary hyperpnoea (EVH), saline, mannitol, methacholine and histamine.

Symptom based diagnosis

The questionnaire, or symptoms based method for the diagnosis of asthma, has been widely employed (see table 2.1), and involves the athlete reporting symptoms of asthma either during or following training or competition. The main symptoms reported are wheezing, cough, tight chest and breathing difficulties; although other symptoms include a mismatch between performance and fitness, problems getting rid of chest infections and difficulties in sleeping (Storms, 1998). These symptoms are usually, but not exclusively seen in asthmatics, and it has been argued that the accompaniment of a physiological test is crucial for the reliable diagnosis of EIA (Boulet et al., 1999). Rundell et al. (2001) examined the accuracy of symptom-based diagnosis of EIA in elite winter athletes. They distributed a questionnaire asking athletes to report symptoms of EIA or asthma following exercise. Each athlete also underwent an exercise challenge. The questionnaire proved to be no more reliable than a 'coin toss' to predict EIA. Of the 41 athletes that presented with EIA following exercise, only 18 (44%) reported more than one EIA symptom. Post-race cough was the most commonly reported symptom for both EIA positive athletes and non-EIA positive athletes. It was concluded that the diagnosis of EIA without a pulmonary function test would yield false positive and false

negative results. This finding supports earlier research (Rundell et al., 2000), and highlights the requirement for a physiological test to confirm diagnosis of EIA.

Direct Airway Challenges

Many studies investigating EIA have used a direct airway challenge as the diagnostic test (Anderton et al., 1979; Avital et al., 1995; Lin et al., 1991; Fourie and Joubert, 1988). The two most common direct airway challenges are histamine and methacholine. Histamine challenges activate smooth muscle and secretory receptors, whereas methacholine is a non-specific cholinergic agonist. Both challenges produce falls in FEV_1 that are proportional to the dose administered. Histamine and methacholine challenges have been previously suggested as more sensitive markers of EIA than exercise (Anderton et al., 1979; Avital et al., 1995; Lin et al., 1991; Fourie and Joubert, 1988). However, the sensitivity and/or specificity of these methods have been challenged. For example, Holzer et al. (2002) screened 50 athletes for EIA using methacholine and EVH challenges and found only 9 (18%) athletes presented with a positive challenge to methacholine, whereas 25 (50%) athletes (including the 9 methcholine positive athletes) presented with a positive EVH challenge. The authors concluded that an EVH challenge was more sensitive and specific than a methacholine challenge for the diagnosis of EIA in athletes. This study concurs with data from previous studies that suggest indirect airway challenges, such as exercise and EVH, are more sensitive and specific in the diagnosis of EIA than direct airway challenges (Haby et al., 1994, 1995; Clough et al., 1991). Thus, the available evidence suggests that direct airway challenges are not sufficiently sensitive or specific for the diagnosis of EIA in athletes and indirect airway challenges are more appropriate.

2.7 Indirect Airway Challenges

Exercise Challenge

Exercise challenges are considered to be the most specific indirect airway challenge used to test athletes for EIA (Anderson et al., 2003; 2005), but their sensitivity has been questioned (Rundell et al., 2004; Mannix et al., 1996). In the past, exercise challenges have been structured so that the athlete completes a bout of exercise that lasts between 6-8 minutes in which they exercise at an intensity of 85% maximum heart rate ((220-age/100) x 85) for at least the final 4 minutes of exercise (Godfery et al., 1975; Konig, 1989; Mahler, 1993; McKenzie et al., 1994). A significant post-test fall in FEV_1 is most likely to be seen 5 to 10 minutes following cessation of exercise (Rundell et al., 2000). Exercise challenges have a high external validity, as the test can be structured to incorporate a sports specific environment, whereas other EIA testing methods are less sport specific. The exercise challenge is also very simple to carry out in the field, as portable spirometry equipment is available for most situations. However, the inability to regulate the duration and $\dot{V}_E$ response during a field-based assessment offers less inter-test reliability and internal validity. Notwithstanding this limitation, Wilber et al. (2000) demonstrated that speed skaters could present with EIA (FEV_1 fall >10%) following a sport specific challenge, which lasted for 1 minute and 20 seconds. Their data led them to conclude that sport specific exercise at near maximal intensity may be more crucial in the identification of EIA, than the duration of the challenge. Exercise challenges should be carried out in the field where possible and the exercise should replicate the athlete's actual event and, where possible, conditions under which, they experience symptoms (Anderson et al., 2005). Criteria for a positive exercise challenge have varied from 7% to 15% falls in FEV_1 from baseline (Wilber et al., 2000; Rundell et al., 2000; Anderson

et al., 1971). However, a fall of 10% in FEV_1 following exercise is the current criterion accepted by the International Olympic Committee – Medical Commission (IOC-MC, 2002).

Early EIA studies incorporating exercise challenges (Anderson et al., 1971) did so in laboratory conditions. However, laboratory conditions do not provide either a sport specific or a cold dry environment that is likely to trigger EIA. Rundell et al. (2000) demonstrated that exercise challenges in the field were more effective than exercise challenges in the laboratory in ambient conditions. They tested 23 elite winter athletes (14 men, 9 women) following exercise challenges in the laboratory and field. Both challenges attempted to mimic the cardio respiratory requirements of competition. 78% of athletes who demonstrated positive tests in the field failed to demonstrate a positive test in laboratory. This study provides evidence that even an exercise challenge conducted at race pace in the laboratory may not provide appropriate conditions to reliably assess elite athletes for EIA.

Eucapnic Voluntary Hyperpnoea (EVH) Challenges

An EVH test is conducted in the laboratory and has a greater level of standardisation and may be more sensitive than an exercise challenge used to diagnose EIA (Rundell et al., 2004). There are two types of EVH challenge: stepped and single staged. The inspirate for both types of EVH challenges is from a compressed gas source that contains 21% oxygen, 5% carbon dioxide, with the balance nitrogen. This concentration of gas is safe, stimulates ventilation, and is thought to maintain normal end-tidal CO_2 levels throughout the challenge. The inspirate is best administered from a gas cylinder via a Douglas Bag (figure 3.3).

A stepped protocol is used mainly in those with severe or unstable asthma. It usually involves three stages of hyperventilation. Stage 1 involves 3 minutes of hyperventilation at 30% maximal voluntary ventilation (MVV) followed by spirometry at 1, 3, 5 and 7 minutes. Stage 2 involves three minutes hyperventilation at 60% MVV followed by spirometry and stage 3 involves threes minutes of hyperventilation at 90% MVV followed by spirometry. If FEV_1 falls ≥20% from baseline after any stage, the test is terminated (Holzer and Brukner, 2004).

The single-stepped EVH test involves a single stage of hyperventilation for 6 minutes at a target ventilation of 85% of MVV, which approximately equals 30 x baseline FEV_1. This is only a target rate and most elite athletes should easily achieve 25 x FEV_1, whereas asthmatics need only breath at 21 x FEV_1 to provoke an airway response (Anderson et al., 2001). Spiering et al. (2004) have suggested 85% of actual maximal minute ventilation is more relevant and reliable than simply multiplying FEV_1 by 30. This however, may not be practical in patients who have not completed a test which measures their maximal minute ventilation.

Eucapnic voluntary hypervpnoea testing has been shown to be more sensitive than exercise in identifying EIA (Rundel et al., 2004; Mannix et al., 1999). A higher number of cases of bronchoconstriction have been diagnosed using EVH challenges than using exercise challenges in the same subjects (Mannix et al., 1999; Rundell et al., 2004). EHV has also been shown to provoke bronchoconstriction in asthmatic non-athletes (Deal et al., 1979). It could therefore be argued that EVH is a more sensitive test for EIA than an exercise challenge and may be a more desirable test for the athlete. Despite this over half the applications for therapeutic use of inhaled β_2-agonists at the 2002 Salt

Lake City Winter Olympic Games used direct airway challenges (Anderson et al., 2003). Despite the greater sensitivity offered by an EVH challenge in the diagnosis of EIA, the EVH test may be fundamentally and practically flawed because 1) it can currently only be carried out in a laboratory 2) it eliminates potential triggers for EIA such as pollen, pollution, and other particulates that may be required to obtain a positive result for EIA 3) the cost of the compressed gas mixture (5% CO_2, 21% O_2) required for EVH test makes the relative cost of an EVH test far greater than other challenges 4) EVH equipment is not widely available and skilled technicians are required to construct an EVH system. Further studies are required to investigate whether exercise or EVH should be used as the main challenge for testing athletes for EIA. An algorithm (figure 2.8) presented recently by Harries and Dickinson (2005) suggests a sport specific exercise should be the first test conducted, followed by an EVH challenge if the initial test is negative and the athlete continues to complain of symptoms. Exercise was suggested as the initial test because of the low cost, specificity and accessibility of the test.

Osmotic Challenges

Osmotic challenges are designed to induce airway hyperosmolarity and hypertonicity without the need to exercise or hyperventilate. They are thought to produce similar levels of hyperosmolarity and hypertonicity to exercise and EVH challenges (Holzer and Brukner, 2004). The two main osmotic challenges are hypertonic saline and inhaled mannitol. The hypertonic saline challenge involves increasing doses of hypertonic saline, either by duration or concentration. Thee mannitol challenge involves the inhalation of increasing doses of a dry powder of mannitol via a Spin Inhaler®. The mannitol challenge may be preferable, as it can be implemented in an office, whereas

the saline challenge must take place in a laboratory. The disadvantage of both tests is that patients are not exposed to exercise or environmental triggers, therefore reducing the test specificity.

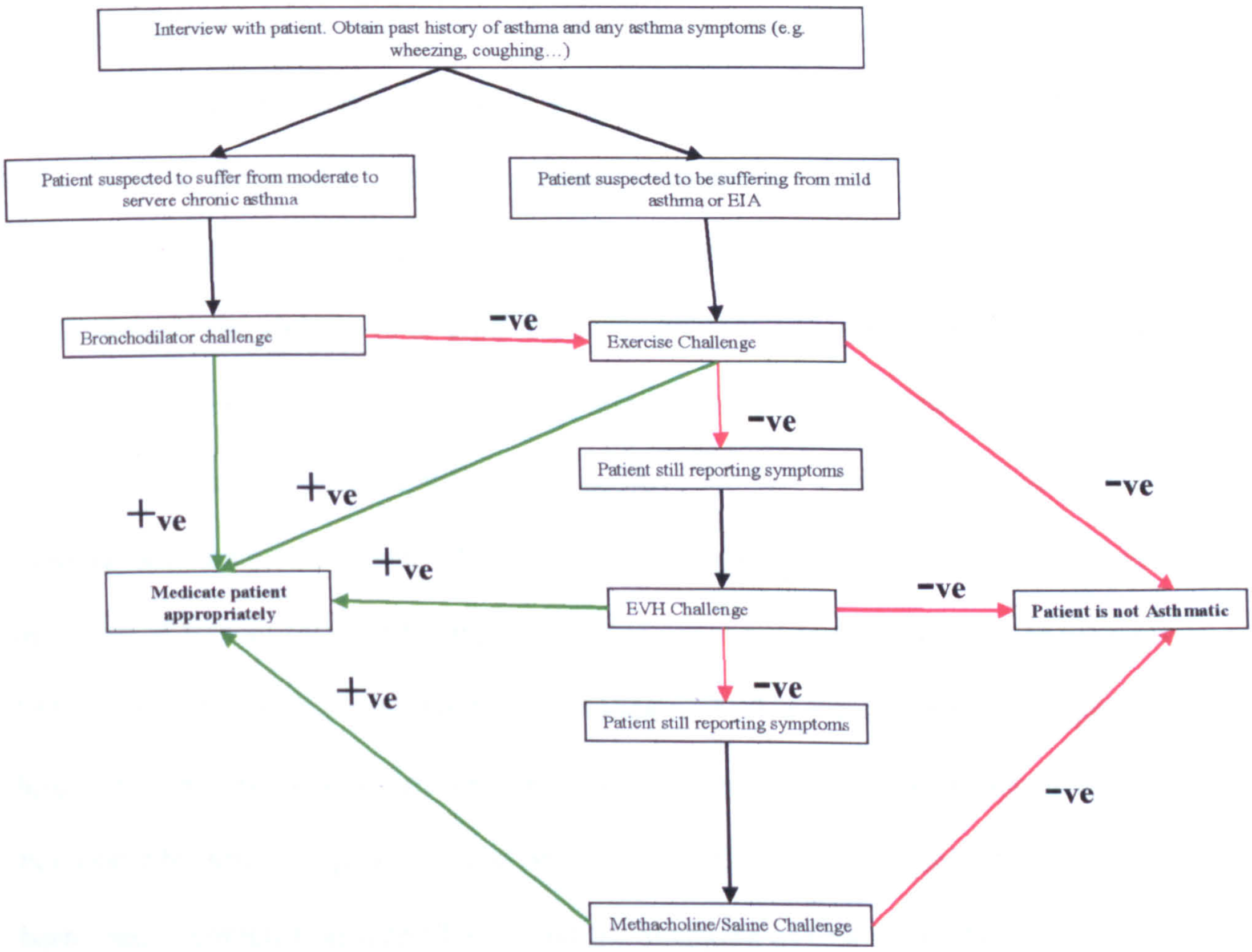

Figure 2.8: Algorithm for EIA Diagnosis

Due to the cost and lack of portability of EVH equipment, a protocol to test an athlete for EIA may consist of first completing a sport specific exercise challenge in those individuals who are already asthmatic or complain of asthma symptoms during or after exercise. If the exercise challenge is negative then an EVH test may be administered on a separate day. (*From Harries, M and Dickinson, J. (2005). 'Exercise Induced Asthma'. In Whyte, G. Harries, M. and William, C. ABC of Sports Medicine 2005. Blackwell publishing, Abingdon UK. P36-39*)

2.8 Diagnostic Criteria

Use of FEV_1 vs Mid-Expiratory Flow Measurements in the diagnosis of asthma

In all EIA tests described above, FEV_1 is the parameter by which changes in maximal expiratory air flow are assessed. To date, however, no 'gold standard' criterion measure of airway function exists for athletes, or non-athletes (Godfrey, 1999). Previous studies using FEV_1 to diagnose EIA have suggested a magnitude of cut off criteria ranging from 7-20% falls in FEV_1 (Anderson et al., 1971; Eggleston et al., 1979; Helenius et al., 1996). Despite the absence of a 'gold standard' criterion measure for diagnosis of EIA in athletes, the International Olympic Committee – Medical Commission (IOC-MC) has ruled that an exercise or EVH challenge is positive for EIA when the FEV_1 falls $\geq$10% from the baseline measurement. The work carried out by Helenius et al. (1996) suggests that a fall of 10% in FEV_1 following an exercise test is not sensitive enough to diagnose EIA in elite athletes. It is possible that the addition of other measurements of expiratory lung function may provide greater sensitivity and specificity in the diagnosis of EIA. For example, forced expiratory flow between 25-75% of vital capacity (FEF_{25-75}) has been used in conjunction with FEV_1 to aid the diagnosis of EIA in children (Custovic et al., 1994; Fonseca-Gouedes et al., 2003) and athletes (Rundell, 2001).

Implicitly, FEV_1 measures expiratory flow at high and mid-lung volumes, whereas FEF_{25-75} and forced expiratory flow at 50% of vital capacity (FEF_{50}) are markers of expiratory flow through middle lung volumes. It has been suggested that FEF_{25-75} and FEF_{50} are more sensitive indicators of airway obstruction in the small airways than FEV_1 (McFaden and Linden, 1972; Lebecaque et al., 1993). Custovic et al. (1994) noted that cut off points for EIA in children (defined as the normal group mean value -2 SD)

occurred with a >10% fall in FEV_1 and >26% fall in FEF_{25-75}. In this study, the combined application of FEV_1 and FEF_{25-75} criteria enabled detection of all subjects with EIA. Furthermore, using both FEV_1 and FEF_{25-75} criteria, none of the subjects with allergic rhinitis or dermatitis presented with EIA. The fall in FEV_1 after exercise in children with allergic rhinitis was within the normal range (≤2SD), but with a significantly lower mean value than control subjects. Thus, the Custovic et al. (1994) study provides promising evidence supporting the addition of mid-expiratory flow-rates to FEV_1 in the diagnosis of EIA in children that might also be applied to the diagnosis of EIA in adults and athletes. To date, there is no literature investigating the sensitivity and specificity of mid-expiratory flow in the diagnosis of EIA in athletic populations.

2.9 Therapy

At present there is no therapy available to cure asthma. However, there are a range of pharmacologic and non-pharmacologic therapies available for asthmatics that reduce the severity of asthma (table 2.3). Highly trained athletes commonly use pharmacologic medication to attenuate EIA. In a recent study of Finnish elite summer-sport athletes, the most commonly used drug was inhaled β_2-agonists (Helenius and Haahtela, 2000). However, despite the widespread use of inhaled pharmacologic therapy by athletes, few randomised, controlled studies have been conducted on their effects on asthma-like symptoms, bronchial responsiveness, or airway inflammation (Helenius et al., 2005).

Recommendations for Therapy

The British Thoracic Society (BTS) has a 5 step guideline (Table 2.4) for asthma treatment in the general population (BTS, 2004). Despite the lack of evidence regarding the treatment of EIA, the BTS (2004) currently recommends inhaled corticosteroids and

inhaled β_2-Agonists as the first line treatments for individuals with EIA. According to the BTS guidelines (2004) inhaled short acting β_2-Agonists should be used in the first instance for mild intermittent EIA (Step 1). If symptoms are not controlled then inhaled corticosteroids should be used in addition (step 2) and then inhaled long-acting β_2-Agonists (step 3) if symptoms are not controlled by the use of both short-acting β_2-Agonists and corticosteroids.

Pharmacologic	**Non-Pharmacologic**
Inhaled short acting β_2-Agonists	Refractory period (Warm-up)
Inhaled long acting β_2-Agonists	Change training environment
Inhaled corticosteroids	Breathing exercises
Oral anti-histamines	Low salt diet
Oral anti-leukotrienes	Poly-unsaturated fatty acids (e.g. fish oils)
Inhaled cromolyn sodium	Anti-oxidants (Vitamin C and E)

Table 2.3: Interventions for EIA

Inhaled β_2-Agonists

In the case of acute break through episodes of asthma, corticosteroids and other similar treatments are ineffective and bronchodilator therapy in the form of β_2-agonists is recommended (Rundell and Jenkinson, 2002). In addition to their use following an acute episode, it is recommended that the short acting β_2-agonist should be inhaled 30 minutes before exercise. This type of treatment has been shown to improve pulmonary function in 90% of individuals with EIA (Anderson et al., 1979). The degree of attenuation to EIA observed following short-acting β_2-agonist administration has ranged

from 50-100% in clinical trials using both adults and children (Anderson et al., 1976; Boulet et al., 1989; Woolley et al., 1990). β_2-agonists relax smooth muscle, increase airflow, decrease vascular permeability and moderately inhibit mediator release (Williams and Shapiro, 1995). Short acting β_2-agonists are not recommended as the only source of treatment for EIA if they are inhaled more than three times a week (BTS, 2004). Further, Anderson and Brannan (2004) suggests that 1) daily use of inhaled β_2-agonists can result in the development of tolerance and reduction in the duration of their protective effect, 2) the severity of EIA may increase when exercise is performed between 8-12 hours following the last inhaled dose and 3) prolonged recovery of lung function after an asthma attack. These responses are believed to be due to desensitisation of the β_2-receptors on mast cells leading to greater mediator release. Since inhaled β_2-agonists are used by a large number of asthmatics in the UK, these findings may have implications for initial therapy given to individuals diagnosed with mild EIA (table 2.4).

Inhaled Corticosteroids

Chronic asthmatic and exercise induced asthmatic individuals who exercise regularly can take medication that controls inflammatory processes and reduces the occurrence of symptoms. A number of studies have demonstrated that treatment with inhaled corticosteroids reduces the number of airway inflammatory cells including mast cells, eosinophils and lymphocytes (Ward et al., 2002), Furthermore, inhaled corticosteroids have been shown to reduce the number of mononuclear cells, $CD4^+$ type 2 T-helper cells (Bocchino et al., 1997). Most studies conducted on inhaled corticosteroids suggest that these effects are usually seen after 2 weeks of treatment (Chanez et al., 2004). Several studies have demonstrated asthmatics using inhaled corticosteroids have an

improved airway epithelium (Lundgren et al., 1988; Laitinen et al., 1992; Heino et al., 1988). However, no single study has demonstrated that inhaled corticosteroids are able to fully restore normality to the airway epithelium layer (Lundgren et al., 1988).

Step	Medication
1 – Mild Intermittent Asthma	Inhaled short-acting β_2-agonists
2 – Introduction of regular preventer therapy	Corticosteroids
3 – Add on therapy	Increase current medication, Inhaled long acting β_2-agonists, theophylines, leukotrienes receptor antagonists, anti-histamines
4 – Poor control on moderate dose of corticosteroid and add on therapy	Add forth drug from list above
5 – Continuous or frequent use of oral corticosteroids	Oral corticosteroids

Table 2.4: The British Thoracic Society 5 Step asthma medication guidelines (*British Thoracic Society. (2004). 'British Guidelines on the Management of Asthma: A national clinical guideline'*)

Despite corticosteroids controlling airway inflammation and remodelling, they do not provide full attenuation to acute airway hyperresponsiveness in all individuals with EIA. For example, it has been demonstrated that treatment with inhaled corticosteroids attenuated acute airway hyperresponsiveness in over 50% of people with EIA (Henriksen and Dahl, 1983; Henriksen, 1985; Vathenen et al., 1991; Farrero et al., 1995). Sue Chu et al. (2000) demonstrated that the corticosteroid budesonide 400mcg,

inhaled twice daily for 12 weeks, had no effect on cellular inflammation in the bronchial mucosa or tenascin expression. However, within the budesonide group, there was a decrease in IL-2 receptor-activated T-helper lymphocytes and an improvement in FEV_1, but asthma symptoms were unchanged in 17 (68%) skiers and methacholine provocation test was negative in 15 subjects, but remained positive in five subjects in each group. However, the improvement in bronchial responsiveness occurred in both treatment and placebo groups and was not accompanied by a decrease in cellular inflammation. In contrast recent studies have shown benefits from regular use of inhaled steroids in patients with mild asthma, even in those whose FEV_1 is >90% predicted (O'Bryne et al., 2001; Pauwels et al., 2003).

2.10 International Olympic Committee – Medical Commision (IOC-MC)

There are conflicting views in recent literature regarding the ergogenic effects of β_2-agonists. Signorile et al. (1992) demonstrated an increase in power output during maximal 15 second efforts on a cycle ergometer after an acute inhalation of the β_2-agonist Albuterol. Bedi et al. (1988) reported an increase in sprint duration at the end of an endurance run after acute inhalation of Albuterol. Another β_2-agonist, Salbutamol, has been shown to increase muscle strength in young men (Martineau et al., 1992). The above studies show that β_2-agonists may be of more benefit to improve performance in short duration high power events (e.g. sprinting, weight lifting) as no improvements in endurance tests have been noted. The research that has specifically looked into the endurance effects of β_2-agonists (Goubault et al., 2001; Meeuwisse et al., 1992) has found no ergogenic effect in elite athletes. Further research is required in this area to clarify the potential ergogenic effects of β_2-agonists as the argument as to the ergogenic effects of the β_2-agonist continues.

Despite the conflicting views on the performance enhancing effects of inhaled β_2-agonists, an asthmatic athlete who competes at the Olympic Games must apply for therapeutic use exemption (TUE) to be allowed to use therapeutic doses of asthma medication (appendix 1 and 2). Prior to the 2002 Salt Lake City Winter Olympic Games an asthmatic athlete only required a doctor's note with an explanation of the athlete's symptoms and the doctors diagnosis and signature. As discussed above, symptoms based diagnosis is neither a sensitive nor a specific diagnosis of EIA and inhaled β_2-agonists are potentially performance enhancing. Due to these reasons, and others listed in table 2.5, the IOC-MC has stated that a simple notification from the team medical officer stating the athlete has EIA is no longer acceptable (IOC-MC 2002). Indeed, a more rigorous testing regime including bronchial provocation and maximal voluntary flow-volume loops is now required (Anderson et al., 2003).

- Large increase in the number of athletes notifying the need to inhale a β_2-Agonist
- Some athlete's may have been mis-diagnosed and did not have asthma/EIA
- Endurance sports seemed to have a higher prevalence of EIA than other sports
- Some evidence that daily use of inhaled β_2-Agonists may result in tolerance to medication
- Geographic distribution of notifications was skewed

Table 2.5: The reasons for IOC-MC change in asthma criteria

(From: *Weiler, J. (2003). 'Why must Olympic athlete's prove that they have asthma to be permitted to take inhaled β_2-agonists?'. Journal of Allergy and Immunology. Vol. 111, pp. 36-37*)

2.11 Summary

In summary asthma is a condition that limits expiratory flow, which is a result of inflammation, smooth muscle contraction and mucosal gland hyper-secretion within the small airways. It is important that individuals who suffer from acute asthma (e.g. exercise induced) obtain accurate diagnosis and optimum therapy to reduce the potential for airway remodelling and worsening of asthma severity. At present reports suggest asthma prevalence within the elite athletes is higher than the general population. Furthermore, the prevalence can vary depending on the training and competitive environment of the sport. However, asthma prevalence data from British elite athletes does not exist.

EIA can be diagnosed by a variety of tests which can be either direct or indirect airway challenges, although, indirect airway challenges are thought to be more sensitive and specific. The IOC-MC accepts data from several different provocation challenges however, it is not clear which indirect challenge is optimal to diagnose EIA within elite athletes. The IOC-MC has criteria for the diagnosis of EIA ($\Delta FEV_1 \geq 10\%$ following either exercise or EVH challenge), which has not been derived from reports on elite athletes and other measures of expiratory flow may provide a more sensitive and specific measure for the diagnosis of EIA in these individuals.

At present there is no therapy available to eliminate asthma. Therefore, there is a range of pharmacologic and non-pharmacologic therapies available for asthmatics that reduce the severity of EIA. BTS guidelines suggest inhaled corticosteroids and β_2-agonists should be used as first line therapy to attenuate EIA. Despite these recommendations

there are limited controlled studies on pharmacologic therapy and attenuation of EIA, in elite athletes.

2.12 Hypotheses

1. H_1 The prevalence of asthma within the British Olympic Team will be reduced at the Athens 2004 Summer Olympic Games when compared to the prevalence at the Sydney 2000 Summer Olympic Games associated with the introduction of the IOC-MC requirement for objective evidence of asthma
2. H_1 The addition of FEF_{50} will provide a greater sensitivity and specificity in the diagnosis of EIA in elite athletes
3. H_1 EVH challenges will have a greater sensitivity than exercise challenges in the diagnosis of EIA in elite athletes
4. H_1 Combination therapy in the form of inhaled corticosteroid and long acting β_2-agonist will provide the greatest attenuation to EIA in elite athletes compared with corticosteroids and long acting β_2-agonist used as individual therapy.

Chapter 3

General Methods

3.1 Spirometry – Maximal Flow Volume Loop

Spirometry is a medical test that measures the volume of air an individual inhales or exhales as a function of time flow. It is an effort dependent manoeuvre that requires co-operation, coordination and understanding by the subject. For these reasons the American Thoracic Society (ATS) has published spirometry guidelines (American Thoracic Society, 1995), which were taken into consideration when spirometry measurements were performed. The ATS guidelines ensure there is a global standard for the manoeuvre and the equipment used to test flow volume that is reliable and specific.

Spirometer

In this following collection of studies all maximal flow volume loops were collected using a MicroLab ML3500 Spirometer (MicroMedical Ltd, Rochester, UK), which met the ATS guidelines for diagnostic spirometers. The volume accuracy of the spirometer was checked daily using a three litre syringe.

Measurement of Maximal Flow Volume Loop

The maximal flow volume manoeuvre (figure 3.1) was conducted as follows. The test was explained to the participant. In preparation for the test the subject was asked about recent illness, medication use, smoking and training they had completed that day. The participant's data was entered into the spirometer and a forced vital capacity manoeuvre was selected. Throughout the whole manoeuvre the participant was asked to remain in a

seated position. Verbal instruction (see table 3.1) and a correct demonstration of the manoeuvre was given. The participant was asked to attach a nose clip and inhale completely. They then placed the mouth piece in there mouth and exhaled maximally until they felt they had reached residual volume. Once they had reached residual volume they were instructed to inspire maximally to total lung capacity. This manoeuvre was completed a minimum of 3 times and no more than 8 times. The maximal flow-volume loop with the best FEV_1 was recorded as long as the second highest FEV_1 was within 0.2L. Each individual maximal flow volume loop effort was accepted if they met the criteria listed in Table 3.2.

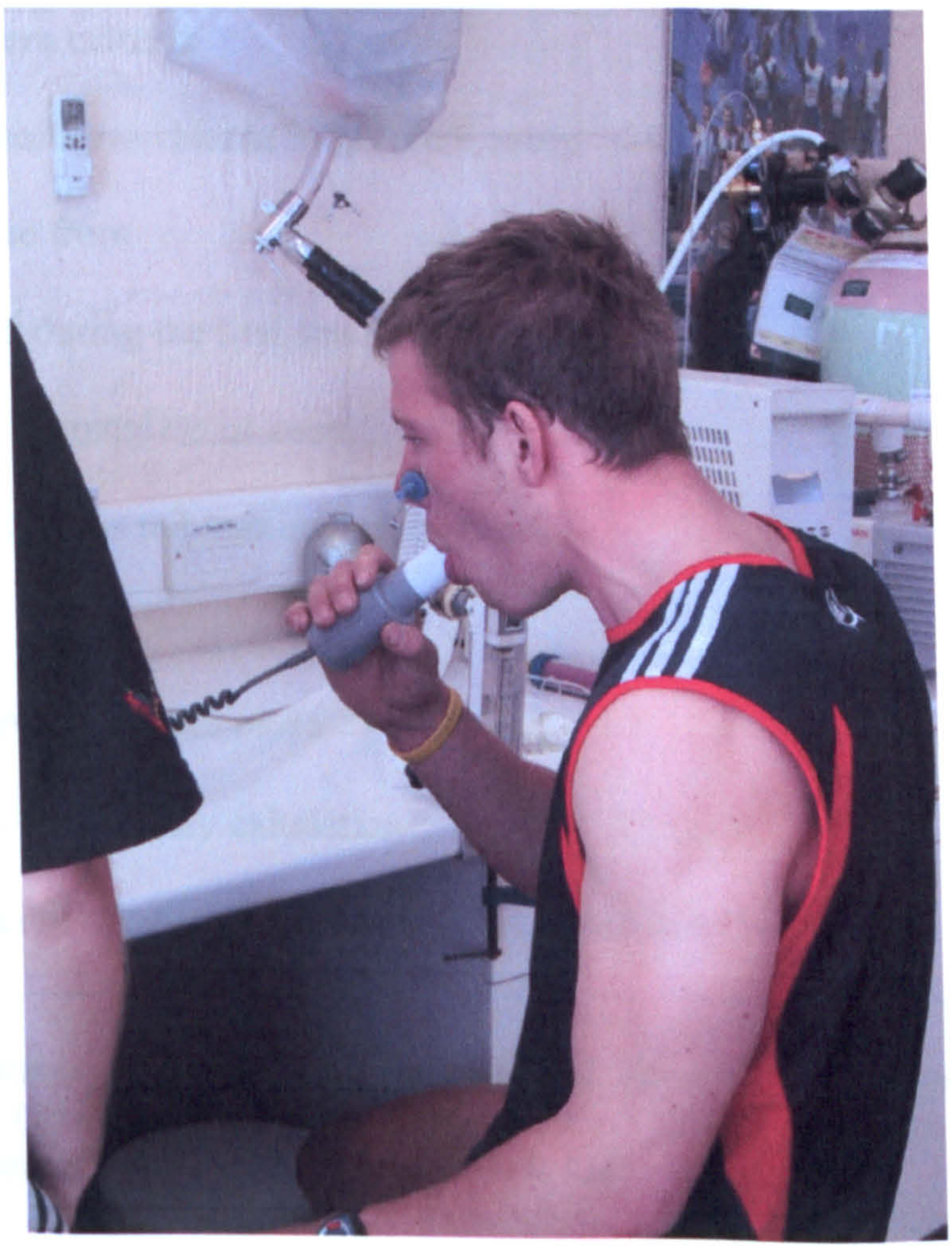

Figure 3.1: Spirometry Measurement

1. Sit up straight and try to be relaxed
2. Place nose clip on
3. Hold the mouth piece to the side of you head
4. Inhale until your lungs are full
5. Place the mouth piece in your mouth and exhale as fast as possible
6. Keep breathing out until you feel your lungs are empty
7. Following complete exhalation keep the mouth piece in your mouth and inhale maximally until your lungs are completely full.

Table 3.1: Verbal instruction given to participant

Within-manoeuvre criteria

Individual maximal flow-volume loops were accepted if:

They are free from

Cough during the first second of exhalation

Early termination or cutcut – off

Effort that is not maximal throughout

Leak

Obstructed mouth piece

They show satisfactory exhalation

Duration of ≥6 seconds or a plateau in volume time curve

Table 3.2: Criteria for acceptance of maximal flow-volume loops (*Adpated from Brusasco, RV. Crapo, R. and Viegi, G. (2005). 'Standardisation of Sprirometry'. European Respiratory Journal, vol. 26, pp. 319-338)*

3.2 Bronchoprovocation Challenge

Bronchoprovocation challenges are used to make the diagnosis of EIA in athletes. In preparation for all bronchoprovocation challenges athletes were instructed to stop pulmonary medications as indicated in table 3.3. The athletes were told not to exercise within 4 hours of the challenge as this may exert a protective effect against EIA (Edmunds et al., 1978; Anderson, 1993). On the day of the test the athletes completed a questionnaire stating any other medication they are using and whether they were suffering from any illness or injury. If an athlete is suffering from an illness or injury that may limit the results of the test, they should be told to return when they are well and fit to complete the test. The athlete was also told not to drink coffee, tea, cola drinks or eat chocolate on the day of the test (Henderson et al., 1993). Following the bronchoprovocation challenge the athlete was not allowed to leave until their FEV_1 was within 10% of their baseline FEV_1. If an athlete had not returned to within 10% of FEV_1 within 15 minutes after stopping the challenge, bronchodilator therapy was offered in the form of inhaled β_2-agonist (e.g. 200mcg Salbutamol).

Bronchoprovocation challenges such as methacholine and histamine were not used to test for EIA as they are not specific to EIA (Mahler, 1993; Haby et al., 1994, 1995; Clough., 1991; Rundell et al., 2002; Holzer et al., 2002). Two challenges that are thought to be specific to diagnose EIA in athletes are: exercise and eucapnic voluntary hyperpnoea (EVH). A positive test for EIA was regarded as a fall of 10% in FEV_1 following either exercise or EVH (ATS, 2000; IOC-MC, 2002).

Medication	**Minimum time interval from last dose to challenge**	**Reference**
Inhaled Short Acting β_2-Agonist	8 hours	Ahrens et al. 1984; Greenspon et al 1984
Inhaled Long Acting β_2-Agonist	48 hours	Derom et al. 1992; Cockcroft and Swystun 1997
Cromolyn Sodium	8 hours	ATS 2000
Leukotriene modifiers	24 hours	ATS 2000
Inhaled corticosteroids	24 hours	Anderson et al 2001

Table 3.3: Time scales for stopping Pulmonary Medication (*adapted from: American Thoracic Society. (2000). 'Guidelines for Methacholine and Exercise Challenge Testing – 1999'. American Journal of Respiratory Critical Care Medicine, vol. 161, pp. 309-329)*

Exercise challenge

Prior to exercise the athlete was instructed to complete three maximal voluntary flow volume loops with the best FEV_1 taken as their baseline value. The athlete then completed exercise in a mode that was sport specific to the athlete (Rundell et al., 2000; 2002). This involved the exercise challenge taking place out side of the laboratory. During the exercise challenge the athlete was asked to work at an exercise intensity that achieved a target heart rate between 80-90% of their max heart rate (HRmax) for approximately 8 minutes. The intensity of exercise during the last four minutes was conducted at $\geq$ 85% of HRmax (ATS, 2000; Joos, 2003). After exercise had stopped the athlete completed maximal voluntary flow-volume loops at 3, 5, 10 and 15 minutes post exercise.

Eucapnic Voluntary Hyperpnoea (EVH) challenge

The EVH challenge (figure 3.2) is a surrogate for exercise to identify EIA in athletes (Anderson et al., 2001). Before the athlete starts the EVH challenge they completed 3 maximal voluntary flow-volume loops with the best FEV_1 being recorded as their baseline measurement. The athlete was then asked to ventilate at a target minute ventilation of 85% of their maximal voluntary ventilation rate (MVV). This was calculated by multiplying their baseline FEV_1 by 30. The air which is inspired during the EVH challenge consists of 21% O_2, 5% CO_2 and 74% N_2 and was delivered via a gas cylinder (see figure 3.3). There is a 5% CO_2 concentration present to prevent syncope during the test. The hyperventilation lasts for 6 minutes during which verbal feedback and encouragement is given to the athlete. During the EVH challenge minute ventilation ($\dot{V}_E$) was monitored by calculating the volume of air passing through the dry gas meter every minute. This allowed the athlete to know whether to increase, maintain or decrease $\dot{V}_E$. After stopping the EVH challenge maximal voluntary flow-volume loops are taken at 3, 5, 10 and 15 minutes.

Figure 3.2: EVH Challenge

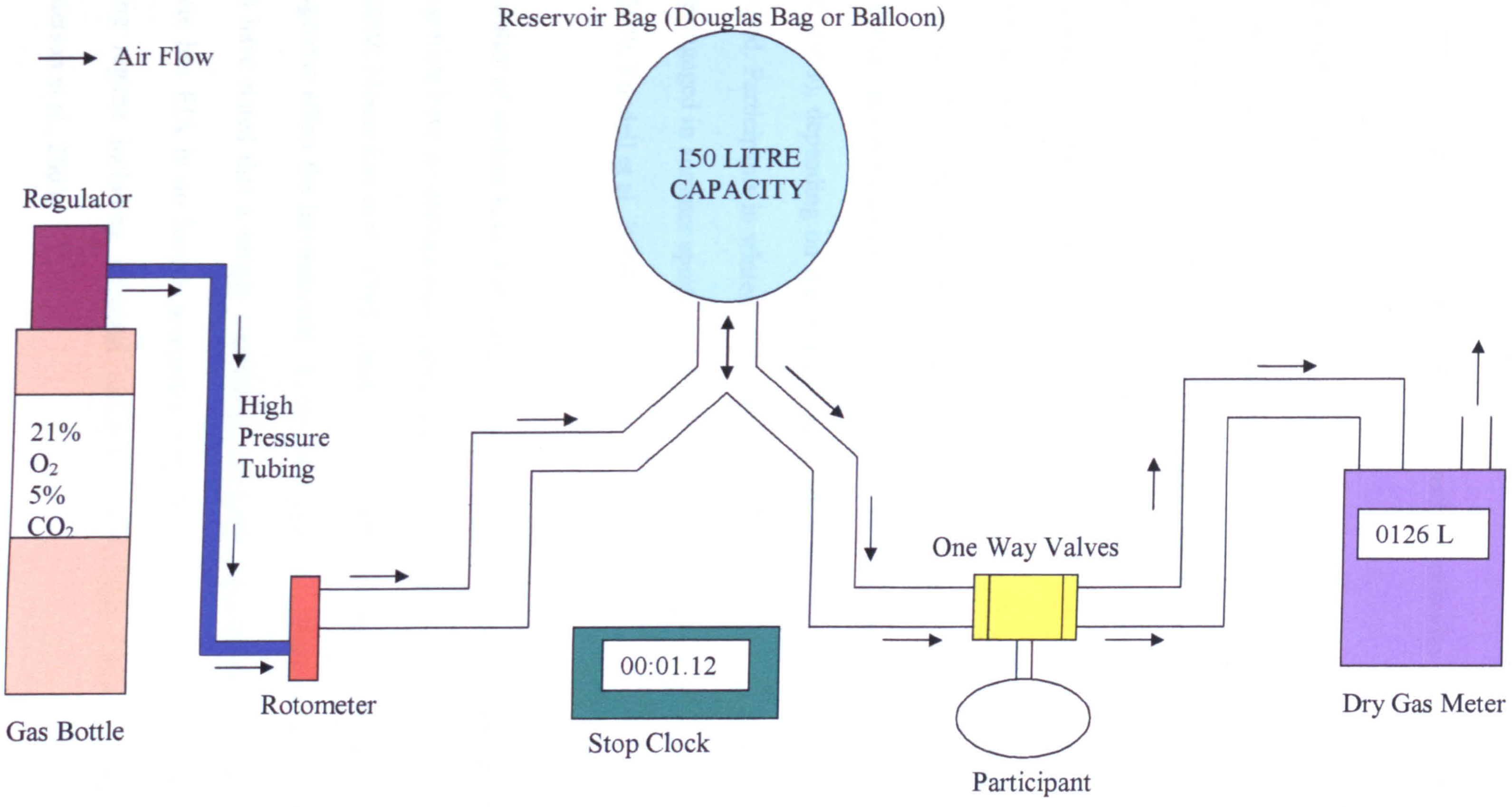

Figure 3.3: Schematic of EVH Equipment.
Note the 5% CO_2 concentration in gas to prevent participant breathing off CO_2 during hyperventilation. The rate the gas passes to the participant is set through the rotometer (30 x FEV_1). The volume of air expired by the participant is recorded at the dry gas meter. Actual breathing rate can be calculated using the stop clock and dry gas meter taking readings every minute. Using the actual rate the participant should be given feedback as to whether they should speed up, maintain or slow down their breathing rate. If the breathing rate is not matched, excess air will collect in the reservoir bag causing the bag to increase in size. A visual goal for the participant can be to not to let the bag fill up with air.

Chapter 4

The Impact of the Changes in the IOC-MC asthma criteria: A British Perspective

4.1 Introduction

Exercise induced asthma (EIA) causes expiratory flow limitation following exercise. It can be triggered by an increase in the volume of 'unconditioned' air inspired through the mouth. During increased levels of activity 'unconditioned' air cools and dries the upper and lower airways inducing inflammation and smooth muscle contraction, which leads to bronchial narrowing (Anderson and Daviskasm 2000) that is readily reversible with inhaled short-acting $ß_2$-Agonists. The prevalence of EIA within athletic populations has been shown to vary between 9%-55% (Hallstrand et al., 2002; Mannix et al., 1999), depending on the type of sport, competitive environment and diagnostic test used. Participants in winter sports generally show a higher prevalence of EIA than those engaged in summer sports (Weiler et al., 1998; Weiler and Ryan, 2000; Wilber et al., 2000; Rundell et al., 2000).

A number of studies have demonstrated that therapeutic doses of inhaled short-acting $ß_2$-Agonists have no performance enhancing effects (Goubault et al., 2001; Collomp et al., 2002; Meeuwisse et al., 1992; Morton et al., 1996). Despite the absence of a proven ergogenetic effect the International Olympic Committee – Medical Commission (IOC-MC) have stated that a simple notification from the team medical officer stating the athlete has EIA is no longer acceptable (IOC-MC, 2002). Indeed, a more rigorous testing regime including maximal voluntary flow-volume loops is now required (Anderson et al., 2003).

One of the main reasons the IOC-MC has given for the enhanced level of evidence required for the use of β_2-Agonists is an apparent increase in the prevalence of asthma observed in athletes since the 1984 Olympic Games (Anderson et al., 2003). At the 1984 Los Angles Olympics, 11% of the United States Olympic team were using inhalers (Voy, 1984). The prevalence of asthma reported within the United States team at the 1996 Olympics in Atlanta was 14% (Weiler et al., 1998), and by 1998 at the Winter Olympics in Nagano this figure had reached 17% (Weiler and Ryan, 2000). Whilst there seems to be a progressive rise in EIA within the United States Olympic teams, there are limited reports of asthma prevalence from other nations' Olympic teams. What remains unclear is whether the observed increase in the prevalence of asthma in the United States teams is an indication of a global trend at elite athletic level. Further, limited data exists examining sport specific prevalence (Rundell, 2004).

Many studies have reported asthma prevalence through the sole use of questionnaires and symptoms (Weiler et al., 1998; Weiler and Ryan, 2000; Voy, 1984; Nysted et al., 2000; Turcotte et al., 2003; Kippelen et al., 2004; Alaranta et al., 2004). This approach, however, is regarded as a poor method of assessment. For example, Rundell et al. (2001) examined the accuracy of symptom-based diagnosis compared to an exercise challenge to diagnose EIA in elite winter athletes by comparing results from an asthma symptoms questionnaire, with those from exercise challenges. Of the 26% participants who tested positive for EIA in response to the exercise challenge, only 40% reported more than one symptom of EIA in the questionnaire. Post-exercise cough was the most common symptom reported by both EIA-positive athletes and EIA-negative athletes. The high number of false positives and false negatives from questionnaire diagnosis

highlights the need for a bronchoprovocation test and supports the IOC-MC requirement for athletes to produce quantitative evidence of their asthma.

The relative paucity of sport-specific data examining asthma/EIA prevalence, together with the IOC-MC criteria changes for asthma diagnosis, provide the rationale for this study. Accordingly the purpose of this study was to compare the prevalence of EIA within the Great British Olympic Team (Team GB) at the 2000 and 2004 Summer Olympic Games, to quantify sport-specific differences in EIA prevalence and to examine the implications of changes made in the IOC-MC guidelines.

4.2 Methods

2004 Team GB

Following local ethics committee approval, British athletes (165 males, 106 females), selected to compete in the 2004 Team GB, were recruited. All athletes were volunteers and provided written, informed consent. Athletes were only tested for asthma if they had a previous diagnosis of EIA or reported symptoms of EIA or were referred for testing by a team medical officer.

IOC-MC Criteria

Diagnosis of asthma for the 2004 Team GB members was made according to the IOC-MC requirements, which included a positive bronchodilator, or bronchoprovocation test. The IOC-MC criteria for positive diagnosis in a bronchodilator challenge were met if the forced expiratory volume in one second (FEV_1) increased 15% or greater following a therapeutic inhaled dose (200mcg) of a short-acting β_2-agonist (Salbutamol). The IOC-MC criteria for positive diagnosis in a bronchoprovocation

challenge were met if the post-challenge FEV_1 dropped 10% or greater from the pre-challenge FEV_1 measurement. Both bronchodilator and bronchoprovocation responses were assessed using maximal effort flow-volume spirometry, measured with an electronic spirometer that met American Thoracic Society guidelines (MicroLab ML3500, Micro Medical, Rochester, UK). The best of three criteria were applied for selection of recordings.

All asthma drug therapy, including inhaled corticosteroids and long acting β_2-agonist therapy, were withdrawn for a minimum of 72 hours before each bronchial challenge. Athletes were advised to use short-acting β_2-agonists if they required any asthma relief during this period.

Bronchodilator Challenge

The bronchodilator challenge involved measuring maximal voluntary flow-volume loops before and 10 minutes following a therapeutic dose (200mcg) of inhaled β_2-agonist (Salbutamol).

Bronchoprovocation Challenges

The Bronchoprovocation challenges consisted of either an exercise challenge or eucapnic voluntary hyperpnoea (EVH) challenge (Anderson et al., 2001).

(i) Exercise

An exercise challenge involved measuring maximal flow-volume loops pre-exercise and at 3, 5, 10 and 15 minutes after stopping exercise. The exercise challenges were conducted for a minimum of 4 minutes and were designed to be as sport-specific as

possible, so could involve running, cycling, rowing or swimming. The target heart rate during the exercise challenge was between 80-90% of maximum heart rate (220-age).

(ii) Eucapnic Voluntary Hyperpnoea

The EVH challenge involved measuring a maximal voluntary flow-volume loops pre-EVH (best of three) and at 3, 5, 10, and 15 minutes after stopping hyperventilation (single effort). The EVH challenge required the athlete to hyperventilate for six minutes at a rate of 30 times their baseline FEV_1 per minute. To prevent hypocapnia during hyperventilation, subjects inspired a gas mix containing 5% CO_2, 21% O_2 and 74% N_2 (Anderson et al. 2001).

2000 Team GB asthma prevalence

Competitors' Medical Forms (120 females; 152 males) from the 2000 Team GB were used to obtain the reported prevalence of asthma before the IOC required quantitative evidence of asthma. Data obtained from these forms included the athletes' asthmatic status and event.

Analysis

The prevalence of asthma within each sport for 2000 Team GB and 2004 Team GB is reported descriptively by sport, gender and overall prevalence.

4.3 Results

Seventy-seven athletes who were members of 2004 Team GB were tested for asthma using a test recognised by the IOC. All athletes required to provide evidence of asthma were tested. Sixty-two of these athletes had been previously diagnosed asthmatic and

were prescribed asthma medication. Thirteen of the 62 (21%) failed to produce a positive test for asthma under IOC criteria. Of these 13 athletes all reported symptoms of EIA with post exercise cough (n=10), wheezing (n=10) and chest tightness (n=10) the most popular. In addition to the 62 medicated athletes, a further 15 athletes, referred by a team medical officer, were tested. Seven of these 15 athletes (47%) tested positive for asthma under IOC guidelines, these athletes had no previous history or diagnosis of asthma. Four of these seven athletes reported symptoms of EIA with post exercise cough (n=3), wheezing (n=3) and chest tightness (n=3) the most common. The athletes who met the criteria to use asthma medication at the 2004 Olympic Games (56 athletes) won a total of 17 medals (7 Gold, 7 Silver, 3 Bronze). The athletes who failed to meet the IOC-MC criteria and were subsequently removed from asthma medication (13 athletes) at the 2004 Olympic Games won a total of two medals (2 Gold).

Of the 56 IOC-MC positive athletes only two athletes provided evidence of asthma through bronchodilator challenge; all other athletes required a bronchoprovocation challenge. The fall in FEV_1 elicited by the positive exercise challenges ranged from 10.5% to 23.3%. The fall in FEV_1 elicited by positive EVH challenges ranged from 10.0% to 61.3%. All athletes who had a positive bronchoprovocation challenge demonstrated reversibility. The prevalence of asthma in the British Olympic Squad at both the 2000 and 2004 is reported in Table 4.1 by gender, sport and overall prevalence.

Swimming had the third highest prevalence of asthma in 2000 (41%) and the highest in 2004 (44%). Sports whose asthma prevalence also remained similar between 2000 and 2004 included canoeing (8% vs 11%), rowing (20% vs 19%) and cycling (44% vs 39%). Sports in which there was a fall in asthma prevalence from 2000 to 2004

included athletics (25% vs 16%), badminton (15% vs 9%), diving (43% vs 14%) and judo (20% vs 13%). Sports that observed an increase in the prevalence of asthma from 2000 to 2004 include archery (33% vs 50%), men's hockey (13% vs 31%), shooting (0% vs 17%) and Tae Kwon Do (0% vs 25%). Sports that had no asthmatics in either 2000 or 2004 included boxing, gymnastics, modern pentathlon, sailing, tennis, triathlon, weightlifting, and wrestling.

		2000			2004		
		n	**No. Asthmatic**	**% Asthmatic**	**n**	**No. Asthmatic**	**% Asthmatic**
Athletics		28	7	25	58	9	16
Badminton		13	2	15	11	1	9
Canoe/Kayak		12	1	8	9	1	11
Cycling		27	12	44	23	9	39
Diving		7	3	43	7	1	14
Gymnastics		14	0	0	9	0	0
Hockey		31	3	10	16	5	31
Judo		10	2	20	8	1	13
Rowing		41	8	20	36	7	19
Sailing		17	0	0	18	0	0
Shooting		6	0	0	6	1	17
Swimming		41	17	41	36	16	44
Triathlon		8	0	0	6	0	0
Other		19	3	16	28	5	18
Overall	**Male**	152	29	19.1	165	34	20.6
	Female	122	29	23.8	106	22	20.8
	Overall	274	58	21.2	271	56	20.7

Table 4.1: British Olympic Squads asthma prevalence at the 2000 and 2004 Olympic Games

4.4 Discussion

The main finding of this study was that the prevalence of EIA in Team GB athletes was unchanged between the 2000 and 2004, whereas within the US Olympic team it appears to be rising (Weiler et al., 1998; Weiler and Ryan, 2000; Voy, 1984). Unfortunately, it is impossible to determine precisely how the US Olympic team diagnoses of asthma were made, as they were conducted at a time when a range of different (unspecified) methods were employed. Data from this study demonstrates that 21% of athletes previously diagnosed with asthma and using inhalers did not meet the IOC-MC criteria. This indicates that a large number of British Olympic athletes were receiving medication for which there was no clinical indication. The percentage of athletes in the 2004 Team GB squad who did not meet IOC-MC criteria is similar to the percentage of athletes whose application was declined by the IOC-MC at the 2002 Winter Olympics (Anderson et al., 2003). Eighteen percent (29 out 159) of those athletes who submitted an application to use β_2-agonists at the 2002 Winter Olympics were refused by the IOC-MC. We support the IOC-MC contention that a large number of athletes may be mis-diagnosed and inappropriately medicated. The new IOC-MC asthma/EIA guidelines may, therefore, improve athlete care.

Despite identifying inappropriately medicated athletes and their subsequent withdrawal from medication, there was no overall change in the prevalence of asthma within Team GB between 2000 and 2004. This outcome is likely due to the identification of the small number (7) of athletes with no previous history, but who presented with a positive response to bronchoprovocation. If diagnosis in the 2004 team had been based upon symptoms alone, the prevalence would have been 27% ([62+12]/271), which is higher than the actual prevalence, and higher than the rate reported in 2000 (21%). This finding

is consistent with previous studies that have demonstrated a continued rise in the asthma prevalence at Olympic Games (Weiler et al., 1998; Weiler and Ryan, 2000; Anderson et al., 2003; Voy, 1984). This data requires substantiation by data from future Olympics using the new IOC-MC criteria.

The results from the present study demonstrate that there is inter-sport variation in the asthma prevalence of Team GB Olympic Teams, with swimming having one of the highest at both the 2000 and 2004 Olympics (>40%). It has been suggested that the high asthma prevalence in swimming may be due to the environment in which swimmers train and compete. The swimming environment has a high concentration of chlorine, which may act as a potent trigger for EIA (Thickett et al., 2002; Nemery, 2002). Other sports such as figure-skating and cross country skiing have also reported a similarly high prevalence of asthma (35%, and 50%, respectively) that has been associated with training and competing in cold and dry, and/or polluted environments (Wilber et al., 2000; Mannix et al., 1996; Rundell et al., 2004). This suggests that athletes who compete in certain sports may be more susceptible to EIA development than others. Data from the present study indicates that the overall prevalence of asthma is higher in elite athletes than it is in the general UK adult population (7.8%) (Asthma UK, 2001). The factors underlying this observation require urgent attention, since they have implications not only for elite athletes, but also for the many recreational athletes in the UK and internationally.

The small number of athletes within some of the Team GB squads (archery, boxing, fencing, modern pentathlon, shooting, tae kwon doe, triathlon) makes it difficult to obtain an accurate impression of the prevalence of EIA/asthma by sport. Indeed, the

prevalence data for triathlon appears to be in opposition to other findings. At the 2000 and 2004 Olympic Games the Team GB triathlon squad did not have one athlete diagnosed with asthma, yet swimming and cycling were amongst the sports with the highest asthma prevalence at both the 2000 and 2004 Olympic Games. It is possible that the absence of asthmatic triathletes within Team GB may be due to the small squad size, and may not be a true representation of triathlon as a whole. Future investigations could overcome this by polling prevalence data from the Olympic Teams of several countries. Multi-centre data collection is indicated to support collection of prevalence data.

In a unique study by Alaranta et al. (2004) sports were classified into four main groups and prevalence of EIA was reported on the basis of whether the sport was endurance, team, speed/power or motor skill. Prevalence of EIA was highest in endurance sports (22.2%) and team sports (14.5%) when compared to speed/power sports (8.8%), and motor skill sports (8.2%). Unfortunately, the study relied solely on physician diagnosis and lacked individual sport prevalence data. Data from the present study used recognised EIA tests to gain the prevalence data at the 2004 Olympics and also examined the individual sports. It is difficult to make a direct comparison with the data from the Alaranta et al. (2004) study, as sports such as swimming and athletics have many different events ranging from sprinting to endurance events. Sub-dividing events into groups based on their aerobic requirement seems to suggest that events with a longer exposure to inhalation of 'unconditioned' air (e.g. endurance events) could have a higher EIA prevalence than events that involve shorter exposure to 'unconditioned' air (e.g. sprint events) supporting the implication of the study by Alaranta et al. (2004). Furthermore, sports/events that take place in environments that have a high potency for triggering EIA (e.g. dry/polluted air) may have the highest prevalence of asthma

regardless of the duration of the activity (e.g. winter sports/swimming). This interpretation suggests that the development of EIA may be exacerbated, or even caused, by a process of airway remodelling in response to training and competing in an environment that triggers EIA. This remodelling process may occur at different speeds, depending on the individual, type of event and environment.

The introduction of more rigorous testing procedures for the diagnosis of EIA/asthma resulted in 21% of athletes who were thought to be EIA-positive being confirmed as EIA-negative. This rate of mis-diagnosis is not as high as that reported by Rundell et al. (2001) in their comparison of questionnaire diagnosis and diagnosis via exercise challenges (60%). One of the reasons for this could be the variety of different methods used to diagnose asthma in previous Team GB athletes. Thus, not all of the athletes who took part in our study would have received previous diagnosis through symptom based diagnosis alone. At present no systematic program exists for diagnosis of EIA/asthma in Team GB athletes. Such a program could reduce the chance of false positive diagnosis, and reduce the needless use of medication, which may have potentially damaging side effects, such as down-regulation of airway β_2 receptors (Anderson and Brannan, 2004). Perhaps more importantly, this study identified seven athletes with no previous history or diagnosis of asthma, three of which reported no symptoms of EIA on questioning. Some of these presented with falls in FEV_1 of greater than 40% following EVH challenge. The implications of untreated EIA/asthma for the performance, health and wellbeing of these athletes can only be speculated upon and argues strongly for the routine screening of all athletes.

4.5 Conclusion

The prevalence of asthma in 2004 Team GB athletes remained similar to 2000 Team GB despite changes in IOC-MC requirements. The improved diagnostic techniques, however, identified a large number of false positive diagnoses, as well as identifying a number of previously unknown asthmatics. These athletes were either removed from unnecessary treatment, or placed on appropriate medication, and therefore received an improved level of care. Screening for EIA within elite athletic populations using bronchoprovocation challenges such as EVH and exercise appears warranted, not only to assist athletes in preparing for major sporting events, but also to ensure the best possible level of care.

Chapter 5

Mid-Expiratory Flow vs FEV_1 Measurements in the Diagnosis of Exercise Induced Asthma in Elite Athletes

5.1 Introduction

Exercise-induced asthma (EIA) occurs in approximately 90% of chronic asthmatics (Lacroix, 1999) and has previously been reported to occur in 7-50% of athletic populations (Weiler et al., 1998; Wilber et al., 2000; Larsson et al., 1993; Helenius et al., 1998). Data presented in chapter 4 demonstrated a prevalence of 21% in Team GB athletes at the 2004 Olympic Games. Asthmatic elite athletes, currently require evidence of asthma to obtain a Therapeutic Use Exemption Certificate, which enables the athlete to use therapeutic doses of inhaled β_2-agonists in and out of competition (IOC-MC 2002). EIA has previously been diagnosed through a variety of challenge methods including; exercise (Rundell et al., 2000; Anderson et al., 1982); eucapnic voluntary hyperpnoea (EVH) (Rundell et al., 2004; Anderson et al., 2003); methacholine (Scanlon and Beck, 1994; Wagner and Jacoby, 1999); histamine (Anderton et al., 1979); hypotonic saline (Smith and Anderson, 1990) and mannitol (Anderson et al., 1997; Brannan et al., 1998). The International Olympic Committee's Medical Commission (IOC-MC) considers positive tests from exercise, EVH, hypotonic saline, histamine and methacholine challenges as evidence of EIA. Methacholine and histamine however, have been shown to be less specific than exercise for EIA diagnosis (Anderson et al., 1997; Avital et al., 1995; Bhagat and Grunstein, 1984). Exercise and EVH challenges are regarded as the most specific methods of EIA diagnosis in elite athletes (Anderson et al., 2003).

In all EIA tests recognised by the IOC-MC, forced expiratory volume in one second (FEV_1) is the parameter by which changes in maximal expiratory function are assessed. At present no 'gold standard' measure exists for the diagnosis of EIA in athletes, or non-athletes (Godfrey, 1999). Previous studies that have used FEV_1 to diagnose EIA have suggested cut off criteria ranging from 7-20% falls in FEV_1 post provocation (Anderson et al., 1971; Eggleston et al., 1979; Helenius et al., 1996). The work carried out by Helenius et al. (1996) suggested that a fall of 10% in FEV_1 following an exercise test is not sensitive enough to diagnose EIA in elite athletes. Despite the absence of a 'gold standard' measure for the diagnosis of EIA in athletes, the IOC-MC has ruled that an exercise or EVH challenge is positive for EIA when the FEV_1 falls $\geq$10% from the baseline measurement.

It is possible that the addition of other measurements of expiratory lung function may provide greater sensitivity and specificity in the diagnosis of EIA. For example, Forced Expiratory Flow between 25-75% of vital capacity (FEF_{25-75}) has been used in conjunction with FEV_1 to aid the diagnosis of EIA in children (Custovic et al., 1994; Fonseca-Guedes et al., 2003) and athletes (Rundell et al., 2000; Rundell et al., 2001). Implicitly, FEV_1 measures expiratory flow at high and mid-lung volumes, whereas FEF_{25-75} and Forced Expiratory Flow at 50% of vital capacity (FEF_{50}) are markers of expiratory flow through middle lung volumes. It has been suggested that FEF_{25-75} and FEF_{50} are more sensitive to airway obstruction in the small airways than FEV_1 (McFadden and Linden, 1972; Lebecaque et al., 1993). Custovic et al. (1994) noted that cut off points for EIA in children (defined as the normal group mean value -2 SD) occurred with a >10% fall in FEV_1 and >26% fall in FEF_{25-75}. In this study, the combined application of FEV_1 and FEF_{25-75} criteria enabled detection of all subjects

with EIA. Furthermore, using both FEV_1 and FEF_{25-75} criteria, none of the subjects with allergic rhinitis or dermatitis presented with EIA. The fall in FEV_1 after exercise in children with allergic rhinitis was within the normal range (≤2SD), but with a significantly lower mean value than control subjects. Thus, the Custovic et al. (1994) study provides promising evidence supporting the addition of mid-expiratory flow-rates to FEV_1 in the diagnosis of EIA in children that might also be applied to elite athletes. The measurements FEF_{50} and FEF_{25-50} are highly correlated and the ratio of the two is reasonably constant. Based on this finding, Bar-Yishay et al. (2003) suggested that reporting both measurements is unnecessary, and suggested that FEF_{50} be the preferred measure. This preference was based upon the argument that FEF_{50} is easily and directly determined, whilst FEF_{25-50} is a calculated parameter that is affected by the spirometer manufactures' choice of algorithm.

At present limited data is available examining the inclusion of mid-expiratory flow for the diagnosis of EIA in elite athletes. The purpose of the present study was to examine the role of FEF_{50} as an adjunct to FEV_1 in the diagnosis of EIA in elite athletes following a bronchoprovocation challenge.

5.2 Methods

Following local ethical committee approval, 66 male (Mean±SD, age 25.1±4.9 years, stature 180.7±7.8 cm, body mass 77.3±12.5 Kg) and 50 female (age 24.3+5.4 years, stature 168.2+7.9 cm, body mass 62.6+9.9 Kg) elite summer and winter athletes, who held either a Gold or Silver British Olympic Association passport (indicating current or potential Olympic competitive standard), volunteered and provided written informed consent for the study. Of the athletes who participated in this study, 83 had a previous

diagnosis of EIA and were using asthma medication. The other 33 athletes had reported symptoms of EIA to a sports physician who had referred them to be tested for EIA. The testing took place at the Olympic Medical Institute, Harrow, between June 2003 and June 2004. Athletes were not tested within two weeks following a respiratory infection or within 12 hours of a training session.

Each athlete completed either an exercise (n=62) or EVH (n=54) challenge. Exercise challenges involved exercising at an intensity of >85% of maximal heart rate for 6-10 minutes in a sport-specific environment (American Thoracic Society 2000). EVH challenges consisted of hyperventilating for 6 minutes at a rate of 85% maximal voluntary ventilation (30 x baseline FEV_1). The gas inspired during the EVH challenge was a medical gas containing 21% O_2, 5% CO_2 and 74% N_2 (Anderson et al., 2001). For both exercise and EVH challenge maximal flow volume loops were measured before and at 3, 5, 10 and 15 minutes after stopping exercise or EVH using a digital spirometer (MicroLab ML3500, Micro Medical Ltd, Rochester, UK) which met ATS guidelines. The lowest values of FEV_1 and FEF_{50} following either exercise or EVH were recorded and the change from baseline was calculated (Δ). A ΔFEV_1 of $\geq$-10% and ΔFEF_{50} of $\geq$-26% were considered cut off criteria for EIA diagnosis (Custovic et al 1994).

Pearson's correlation was used to calculate the relationship of ΔFEV_1 and ΔFEF_{50}. Specificity, sensitivity, predictive value of positive test and efficiency were calculated for FEF_{50} cut-off criteria of 26% and 14%.

5.3 Results

There was a strong positive correlation between ΔFEV_1 and ΔFEF_{50} following bronchoprovocation ($r=0.94$, $p=0.000$) (see figure 5.1). Sixty athletes (52%) demonstrated a ΔFEV_1 of $\geq 10\%$ leading to the diagnosis of EIA (see figure 5.1). Using the FEF_{50} criteria alone led to 21 (35%) asthmatic athletes receiving false negative diagnosis; thus, 39 athletes met both FEV_1 and FEF_{50} criteria. The lowest ΔFEF_{50} in an athlete with a $\geq 10\%$ fall in FEV_1 was -14.3%. Reducing the FEF_{50} criterion to a $\geq -14\%$ fall included 13 athletes whose ΔFEV_1 was not $\geq 10\%$ (mean $\Delta FEV_1 = 5.7$, range -8.9 to -1.5) (see figure 5.1). Only one athlete had a $\geq 26\%$ fall in FEF_{50} in the absence of a $\geq 10\%$ fall in FEV_1 ($\Delta FEV_1 = 8.9\%$).

Of the 83 athletes with a previous diagnosis of EIA, 33 athletes failed to present evidence for the diagnosis of EIA ($\Delta FEV_1 < 10\%$) following the bronchoprovocation challenge. Of the 33 athletes who had been referred for testing but had no previous diagnosis of EIA, 10 athletes presented with EIA following bronchoprovocation

The values for FEF_{50} and FVC pre and post bronchoprovocation challenge for the asthmatic and non-asthmatic groups are reported in table 5.1. FEF_{50} ($p=0.000$) and FVC ($p=0.000$) are significantly lower post bronchoprovocation in the asthmatic athletes. There was no significant change in FEF_{50} or FVC pre and post bronchoprovocation challenge in non-EIA athletes ($\Delta FEV_1 \leq 10\%$).

The specificity, sensitivity, predictive value of positive test and efficiency for FEF_{50} cut-off criteria of 26% and 14% are reported in tables 5.2, 5.3 and 5.4, respectively.

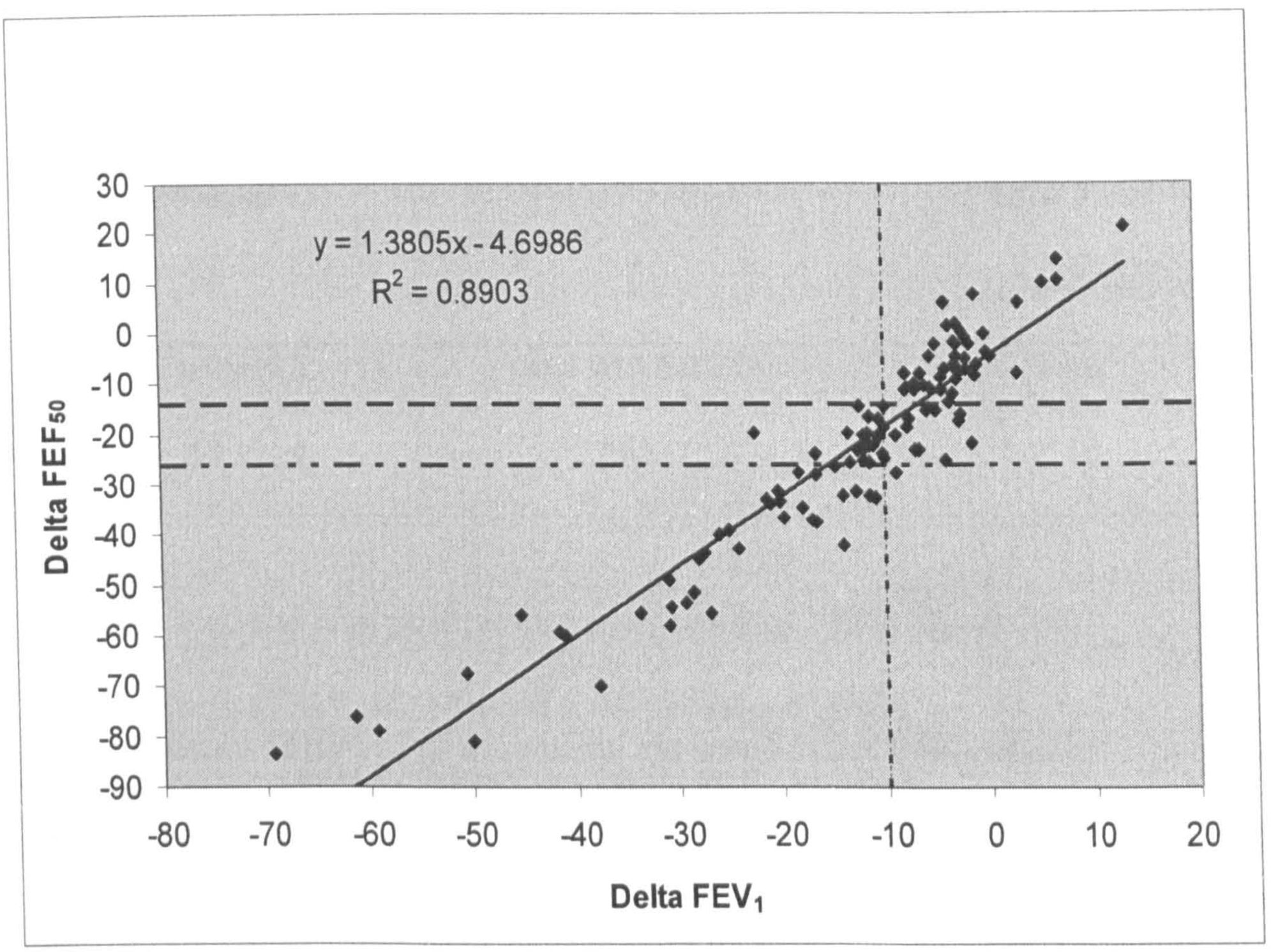

Figure 5.1: Delta FEV_1 vs. Delta FEF_{50}

	FEF_{50} (l/s)		FVC (l)	
	Pre (mean±SD)	Post (mean±SD)	Pre (mean±SD)	Post (mean±SD)
Asthmatic	3.86±0.92	2.39±0.84**	4.99±1.00	4.45±1.16**
Non-Asthmatic	4.79±1.37	4.43±1.31	4.81±1.03	4.65±1.04

Table 5.1: Changes in FEF_{50} and FVC following bronchoprovocation challenge

Asthmatic athlete defined as having a ≥10% fall in FEV_1 following bronchoprovocation.

**= significantly different ($p<0.05$) from pre test value

True positive	True Negative	Total True
39	55	94
False Negative	False Positive	Total False
21	1	22
Total with EIA	Total without EIA	Total
60	56	116

Table 5.2: True and false positive diagnoses based on FEF_{50} cut-off 26%

True Positive = ΔFEV1 of ≥10% and a fall in FEF_{50} of ≥26%
True Negative = ΔFEV1 of ≤10% and did not have a fall in FEF_{50} of ≥26%
False Positive = ΔFEV1 of ≤10% and a fall in FEF_{50} of ≥26%
False Negative = ΔFEV1 of ≥10% and a fall in FEF_{50} of ≤26%

True positive	True Negative	Total True
51	43	94
False Negative	False Positive	Total False
9	13	22
Total with EIA	Total without EIA	Total
60	56	116

Table 5.3: True and false positive results based on FEF_{50} cut-off 14%

True Positive = ΔFEV1 of ≥10% and a fall in FEF_{50} of ≥14%
True Negative = ΔFEV1 of ≤10% and did not have a fall in FEF_{50} of ≥14%
False Positive = ΔFEV1 of ≤10% and a fall in FEF_{50} of ≥14%
False Negative = ΔFEV1 of ≥10% and a fall in FEF_{50} of ≤14%

	Cut-off criteria of 26%	Cut-off criteria of 14%
Specificity *	98	77
Sensitivity &	65	85
Predictive value of positive test ~	98	80
Efficiency #	81	81

Table 5.4: The Effectiveness of FEF_{50} cut-off criteria of 26% and 14%.

*=True Negative / (True negative + True positive)
&=True Positive / (True positive + False Negative)
~=True Positive / (True positive + False Positive)
#= (True Positive + True Negative) / Total Number of tests

5.4 Discussion

Data from the present study demonstrates that the addition of FEF_{50} reduces the sensitivity of EIA diagnosis, following exercise or EVH challenge. Of the 60 athletes who were diagnosed with EIA using IOC-MC criteria of a ≥10% fall in FEV_1, 21 (35%) athletes would have received false negative diagnosis if a combination of FEV_1 and FEF_{50} falls were required for diagnosis. Furthermore, only one athlete exceeded the criterion for FEF_{50}, but not for FEV_1. Our study therefore suggests FEF_{50} does not improve the sensitivity or specificity for the diagnosis of EIA in elite athletes via the IOC-MC criteria ($\Delta FEV \geq 10\%$).

In previous studies, measurements of FEF_{25-75} have been employed to supplement FEV_1 in the diagnosis of EIA in children (Custovic et al., 1994; Fonseca-Guedes at al., 2003) and athletes (Rundell et al., 2000; Rundell et al., 2001). The studies conducted on

children have supported the addition of FEF_{25-75} measurements to improve the diagnosis of EIA. It has been suggested FEF_{25-75} is a more sensitive measure of obstruction in the small airways than FEV_1 (McFadden and Linden, 1972). Thus, EIA may be a disease that consistently affects expiratory flow through the small airways. Fonseca-Guedes et al. (2003) noted that only 60% of children with 'intermittent' EIA compared to 94.4% of children with 'severe persistent' EIA met the criteria for both FEV_1 and FEF_{25-75}. Fonseca-Guedes et al. (2003) suggest FEF_{25-75} was more likely to fall significantly than FEV_1 in children with mild EIA. In contrast, our data are inconsistent with this finding and suggest that FEV_1 is more likely to fall significantly in athletes with mild asthma. Indeed, only 1 athlete had a significant fall in FEF_{50} (≥26%) in the absence of a significant fall in FEV_1, compared to 21 athletes who had a significant fall in FEV_1 (≥10%) in the absence of a significant fall in FEF_{50} (≥26%). Only 39 athletes met both criteria for FEF_{50} and FEV_1, which would have resulted in 21 (35%) of athletes (who met FEV_1 criteria) receiving a false negative diagnosis for EIA. The reduced sensitivity demonstrated following the inclusion of FEF_{50} measurement suggests that, in elite athletes with mild EIA, expiratory airflow is just as likely to be restricted in the larger airways as it is in the smaller airways. Thus, it is most appropriate to assess expiratory flow using an index of function for both the larger and smaller airways of the lung, i.e. FEV_1.

There have been a number of studies conducted examining the diagnosis of EIA in athletes; however, these have not specifically used mid-expiratory flow rates as a criterion measurement to diagnose EIA. Rundell et al. (2000) suggested that a fall in FEF_{25-75} of 14% is significant in the diagnosis of EIA in winter athletes. This lower limit was calculated by taking the mean post exercise change from baseline spirometry

and subtracting 2 standard deviations. Lowering the FEF_{50} cut-off criterion in our data to ≥14% resulted in an increase in the sensitivity, however, this came at a cost of a lower specificity of the measurement, from 98% to 77%. Using a ≥14% criterion, 13 athletes would have been diagnosed EIA who did not meet the IOC-MC criterion of a 10% fall in FEV_1 from baseline values.

A further problem associated with the use of FEF_{50} as a criterion measurement is that its reliability is dependent upon constancy of FVC. The data from this study demonstrate that the mean fall in FEF_{50} following bronchoconstriction was accompanied by a mean fall in FVC in EIA athletes. Therefore, the fall in FEF_{50} that is evident in some of the athletes following a bronchoprovocation test may be partially attributable to a reduction in FVC. Small falls in FVC will not effect the FEV_1 measurement. The reduction of FVC in asthmatic athletes may be due to the prolongation and discomfort associated with exhaling to residual volume during bronchoconstriction. Despite standard controls, this may cause the athlete to stop exhaling prior to reaching residual volume. This shortcoming further undermines the potential value of FEF_{50} for diagnosis of EIA.

5.5 Conclusion

The addition of FEF_{50} to FEV_1 reduces the sensitivity of EIA diagnosis in elite athletes. Our data suggest that a more global measure of maximal expiratory airflow (FEV_1) provides the most sensitive and specific diagnosis of EIA, especially when the severity of the disease is thought to be mild. This would suggest that EIA is a disease that is associated with expiratory flow limitation in the larger and smaller airways of elite athletes. However, methodological issues associated with assessment of FEF_{50} (reliance upon FVC) mean that this interpretation should be viewed cautiously. Future studies

should investigate the efficacy of the IOC-MC criterion of a 10% fall in FEV_1 to define a more statistically justified cut-off point for EIA diagnosis in elite athletes and examine the most appropriate diagnostic tool i.e. EVH vs exercise either based in the lab or sport specific environment to establish EIA in elite athletes.

Chapter 6

Screening Elite Winter Athletes for Exercise-Induced Asthma: A Comparison of Three Challenge Methods

6.1 Introduction

The reported prevalence of exercise induced asthma (EIA) in winter athletes ranges from 9% to 50% (Wilber et al., 2000), which is higher than that of the general population (e.g., approximately 8% in the UK), but in line with estimates for elite summer sports athletes (see chapter 4). At both the 2002 Salt Lake City Winter Olympics and the 2004 Athens Summer Olympics, athletes who wished to use inhaled β_2-agonists therapeutically were required to provide evidence of asthma through bronchodilator or bronchial provocation challenges. At present, there is no 'gold standard test' for EIA, however the International Olympic Committee-Medical Commission (IOC-MC) accepts the results of a number of different airway challenges, including exercise, eucapnic voluntary hyperpnoea (EVH), methacholine and saline challenges (Anderson et al., 2003).

Exercise is an indirect airway challenge that has a high level of specificity (Anderson et al., 2003), but its sensitivity is affected by environmental conditions (Rundell et al., 2000). Accordingly, exercise challenges in sport-specific (SS) environments may be more sensitive than exercise challenges conducted in laboratory (LB) settings (Rundell et al 2000). This is most likely because the air-conditioned laboratory environment has a relatively high temperature and water vapour content (i.e. Temperature c.20°C, Humidity c.50%). Airway drying (Anderson, 1984; Anderson and Daviskas, 2000;

Evans et al., 2005; Hahn et al., 1984; Holzer et al., 2002) and airway cooling (McFadden et al., 1986) have been proposed as mechanisms in the aetiology of EIA. Therefore, an air conditioned LB environment may not be sufficiently provocative, especially for winter athletes, who train and compete at sub-zero temperatures, where the water vapour content of the air is very low. Despite this limitation, LB exercise challenges are still used to assess elite athletes for EIA.

Eucapnic voluntary hyperpnoea (EVH) is a laboratory based indirect airway challenge that enables minute ventilation and environmental conditions to be controlled. The EVH challenge has been reported to be the most suitable method for the diagnosis of EIA in cold weather athletes (Mannix et al., 1999; Rundell et al., 2004). However, over half of the requests for therapeutic use exemption (TUE) for β_2-Agonists submitted for the 2002 Salt Lake City Winter Olympics employed direct airway challenges to establish EIA (i.e. methacholine and histamine) (Anderson et al., 2003). The sensitivity and/or specificity of these methods have been challenged. Holzer et al. (2002) screened 50 athletes for EIA using methacholine and EVH challenges and found only 9 (18%) athletes presented with a positive challenge to methacholine, whereas 25 (50%) athletes (including the 9 methacholine positive athletes) presented with a positive EVH challenge. The authors concluded that an EVH challenge was more sensitive and specific than a methacholine challenge for the diagnosis of EIA in athletes. Thus, evidence suggests that direct airway challenges are not sufficiently sensitive or specific for the diagnosis of EIA in athletes.

Due to the lack of sensitivity and specificity of symptom based diagnosis (Rundell et al., 2001) and direct airway challenges (Holzer et al., 2002) several groups have

recently suggested that athletes should be screened for EIA using either EVH challenge, or exercise challenges (Bokulic, 2002; Holzer and Brukner., 2004; Helenius et al., 1996; Kukafka et al., 1998; Rupp et al., 1992; Rupp et al., 1993). At present, however, limited evidence exists examining the sensitivity and specificity of eucapnic voluntary hyperventilation challenge and laboratory based and sport specific exercise challenges in elite athletes. The aims of this study were to establish whether an asthma screening program would be beneficial for elite British winter athletes and examine the role of the EVH challenge and laboratory based (LB) and sport specific (SS) exercise challenges in the evaluation of elite winter athletes.

6.2 Methods

Following ethical approval from Harrow Local Research Ethics committee, 14 athletes (mean±SD; age 22.6±5.7years, height 177.2±7.0cm, weight 68.9±16.9kg) from the Great Britain Short-track Speed Skating (n=10) and Biathlon (n=4) teams volunteered and provided written informed consent.

Each athlete completed a laboratory based challenge (LB), a sport-specific challenge (SS), and a eucapnic voluntary hyperventilation challenge (EVH) in a random order. All asthma drug therapy, including inhaled corticosteroids and long acting β_2-agonist therapy, were withdrawn for a minimum of 72 hours before each bronchial challenge. Athletes were advised to use short-acting β_2-agonists if they required any asthma relief during this period, until 8 hours before the challenge.

Laboratory based exercise (LB) challenge

The LB challenge required the athlete to run continuously on a treadmill for 8 min (Temperature 18°C, Humidity 56%). Exercise intensity was set to illicit a HR greater than 90% HR_{max} for the final four minutes of exercise (Joos and O'Conner, 2003).

Sports Specific exercise (SS) challenge

The SS challenge for the speed skaters involved skating for 6 min (pace ranged between 11-12 seconds per 250m lap) on the ice-rink (Temperature 8°C, Humidity 35% H_2O content). The SS challenge for the biathletes involved a 20min simulated race in Vaukati, Finland (Temperature. 1-2°C, Humidity 31-34% H_2O).

Eucapnic Voluntary Hyperventilation (EVH)

The EVH challenge was conducted in the laboratory and required each athlete to hyperventilate for 6 min (30 x baseline FEV_1) breathing a gas mixture containing 5% CO_2, 21% O_2, 74% N_2 (Inspired Air Temperature 19.1°C, Humidity <2%) (Anderson et al., 2001).

A MicroLab ML3500 (Micro Medical Ltd, Rochester, UK) spirometer was used to collect all spirometry measurements. Maximal effort voluntary flow-volume loops were measured before and at 3, 5, 10 and 15 minutes after stopping each challenge. Forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), forced vital capacity (FVC), forced expiratory flow at 50% of FVC (FEF_{50}) and FEV_1 as a percentage of FVC (FEV_1%) were recorded at each time point.

The percentage change (Δ) in FEV_1, PEF, FVC, FEF_{50} and FEV_1% were calculated for each challenge by taking the lowest value recorded in the 15 minutes following each challenge and expressing the difference between this and the baseline value measured immediately before each challenge as a percentage. A fall in FEV_1 of 10% or greater from the baseline value was deemed positive for EIA.

Statistics

Repeated measure analysis of variance (ANOVA) tests were used to compare the changes in ΔFEV_1, ΔPEF, ΔFVC, ΔFEF_{50} and ΔFEV_1% for each challenge. Planned unpaired t-tests were used to analyse the difference between positive and negative athletes for each challenge. A *P* value of <0.05 was regarded as significant. All values are presented as mean $\pm$ SD.

6.3 Results

All 14 athletes completed every challenge. Of 14 athletes, 2 athletes had a previous history of asthma and were currently medicated with beclomethasone and salbutamol inhalers. Baseline lung function and ΔFEV_1 for each challenge are reported for every athlete in table 6.1.

Based on a $\geq$10% fall in FEV_1, 10 of the 14 athletes (including two athletes with a previous history of asthma) had a positive test to at least one of the challenges (see Table 6.1). There was no difference for percent predicted baseline FEV_1 values between positive (102.9$\pm$11.43%) and negative (110.3$\pm$12.6%) EIA athletes. Ten athletes had a positive response to EVH; of these, only 3 also had a positive response to the SS

challenge. No athletes had a positive test to the LB challenge (see figures 6.1, 6.2 and 6.3).

After the assumption of sphericity was met, repeated measures ANOVA revealed ΔFEV_1 (P=0.001), ΔPEF (P=0.001), ΔFEF_{50} (P=0.001) and $\Delta FEV_1\%$ (P=0.001) changes were significantly greater following EVH than either the LB or SS challenge. The average falls for positive ($\Delta FEV_1 \geq 10\%$ for at least one challenge) and negative athletes following LB, SS and EVH challenges are reported in table 6.2.

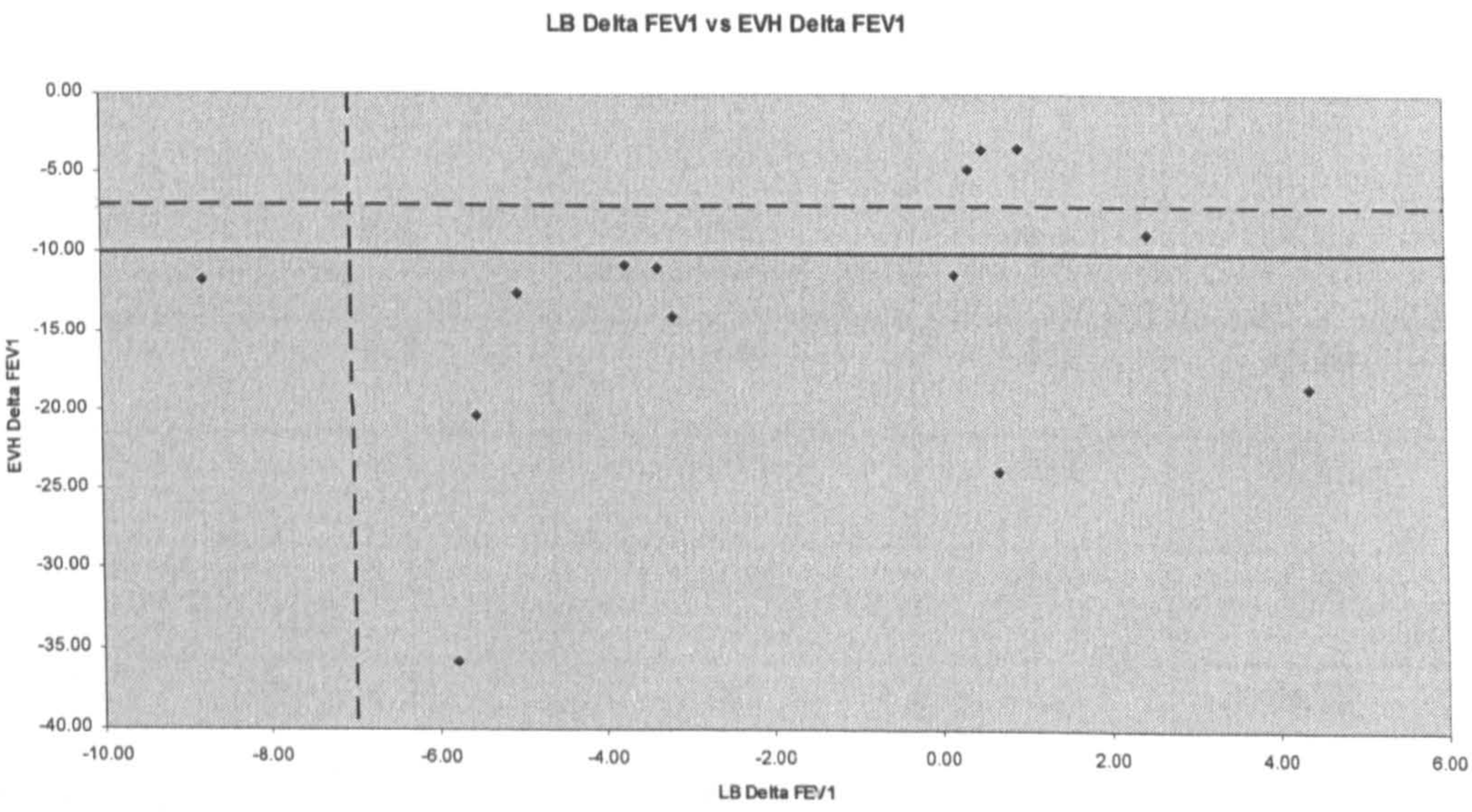

Figure 6.1: LB challenge vs EVH challenge

Athlete No.	Baseline FEV_1 (l)	% of predicted FEV_1 (%)	SS ΔFEV_1 (%)	LB ΔFEV_1 (%)	EVH ΔFEV_1 (%)
1	**4.8**	**104**	**-13.9**	**-5.52**	**-20.3**
2	4.0	126	-2.5	2.48	-8.8
3	**4.5**	**113**	**-20.7**	**-5.77**	**-35.8**
4	**4.5**	**104**	**-3.4**	**-3.34**	**-11.0**
5	**4.5**	**96**	**-1.1**	**-3.15**	**-14.0**
6~	**4.8**	**100**	**-14.7**	**-8.78**	**-11.8**
7	**4.0**	**113**	**-2.5**	**-3.72**	**-10.8**
8	4.1	97	2.4	0.97	-3.4
9	4.0	114	-7.2	0.53	-3.5
10~	**3.6**	**79**	**-9.1**	**-5.01**	**-12.5**
11#	**4.7**	**104**	**-4.1**	**0.20**	**-11.4**
12#	5.1	104	-8.2	0.38	-4.7
13#	**5.1**	**120**	**-2.9**	**4.38**	**-18.4**
14#	**4.1**	**96**	**-1.5**	**0.70**	**-23.7**
Mean ±SD	4.4±0.4	105±11.8	-6.4±6.4	-1.8±3.7	-13.6±8.7

Table 6.1: Athlete responses to each challenge

LB ΔFEV_1= change in FEV_1 following Laboratory Based exercise challenge
SS ΔFEV_1= change in FEV_1 following Sport Specific exercise challenge
EVH ΔFEV_1= change in FEV_1 following Eucapnic Voluntary Hyperventilation challenge
EIA positive athlete identified by **bold print**
~ = past history of asthma and regular therapy using bechlomethosone and salbutamol
#= Member of the British Biathlon Team
Predicted values = European Community for Coal and Steel (1993)

		LB		SS		EVH	
		No.	Δ	No.	Δ	No.	Δ
FEV_1 *+	Positive	0		3	-16.4±3.73	10	-16.9±7.99
	Negative	14	-1.83±3.73	11	-3.6±3.39	4	-5.1±2.51
PEF *	Positive	0		3	-14.4±4.38	10	-14.9±7.49
	Negative	14	-2.32±4.39	11	-2.9±5.87	4	-7.08±7.09
FVC	Positive	0		3	-7.7±2.08	10	-3.1±3.37
	Negative	14	-2.44±2.26	11	-3.9±4.00	4	-1.7±2.59
FEF_{50} +	Positive	0		3	-24.6±3.79	10	-30.7±10.13
	Negative	14	-2.44±13.38	11	-2.9±17.90	4	-14.2±9.93
FEV_1% *+	Positive	0		3	-9.5±2.17	10	-14.4±6.56
	Negative	14	0.65±3.96	11	0.4±4.09	4	-3.41±2.69

Table 6.2: Comparison of mean percentage changes for EIA-positive and EIA-negative athletes for the EVH and SS challenges.

*= Significant difference *(P≤0.05)* between positive and negative athletes following SS
+= Significant difference *(P≤0.05)* between positive and negative athletes following EVH

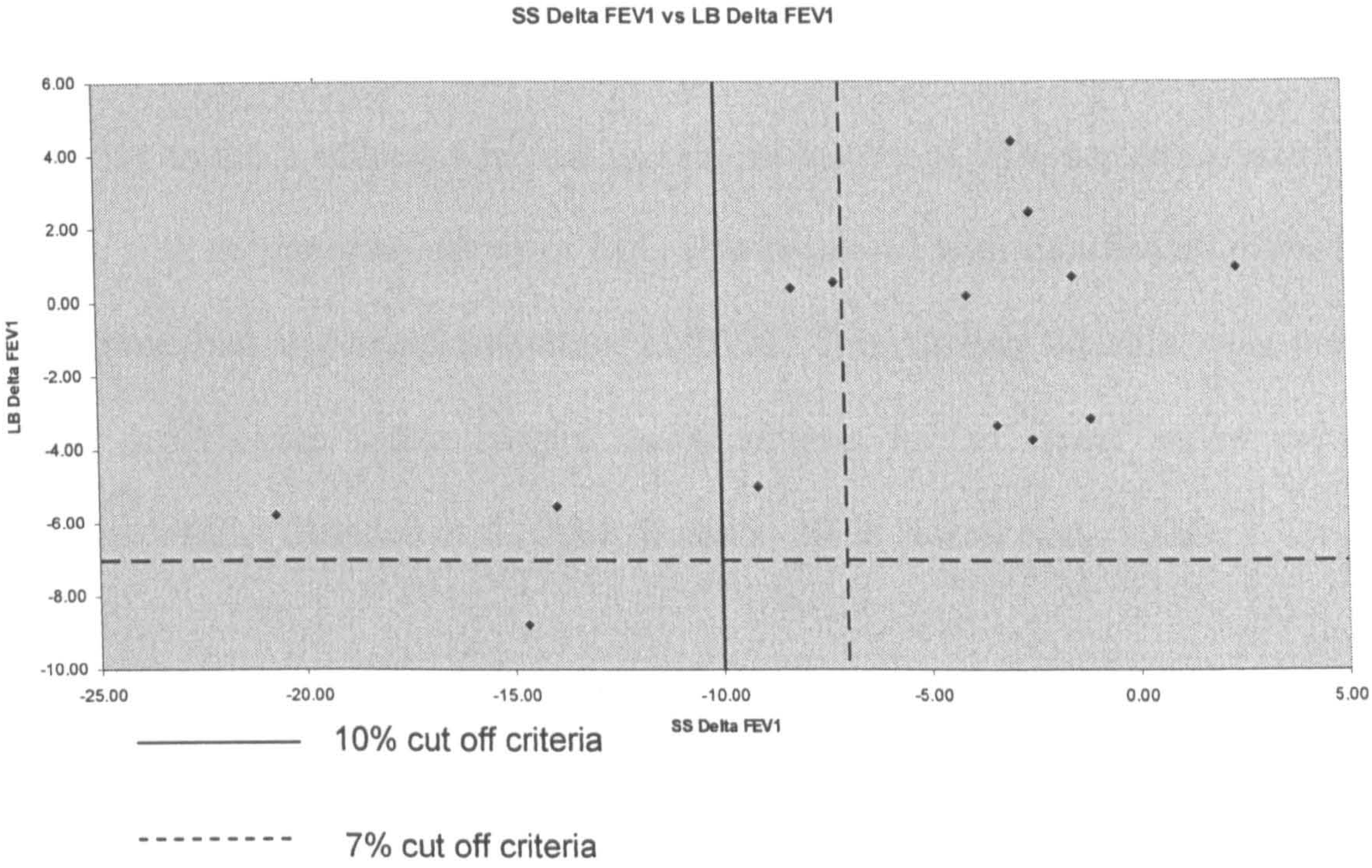

Figure 6.2: LB challenge vs SS Challenge

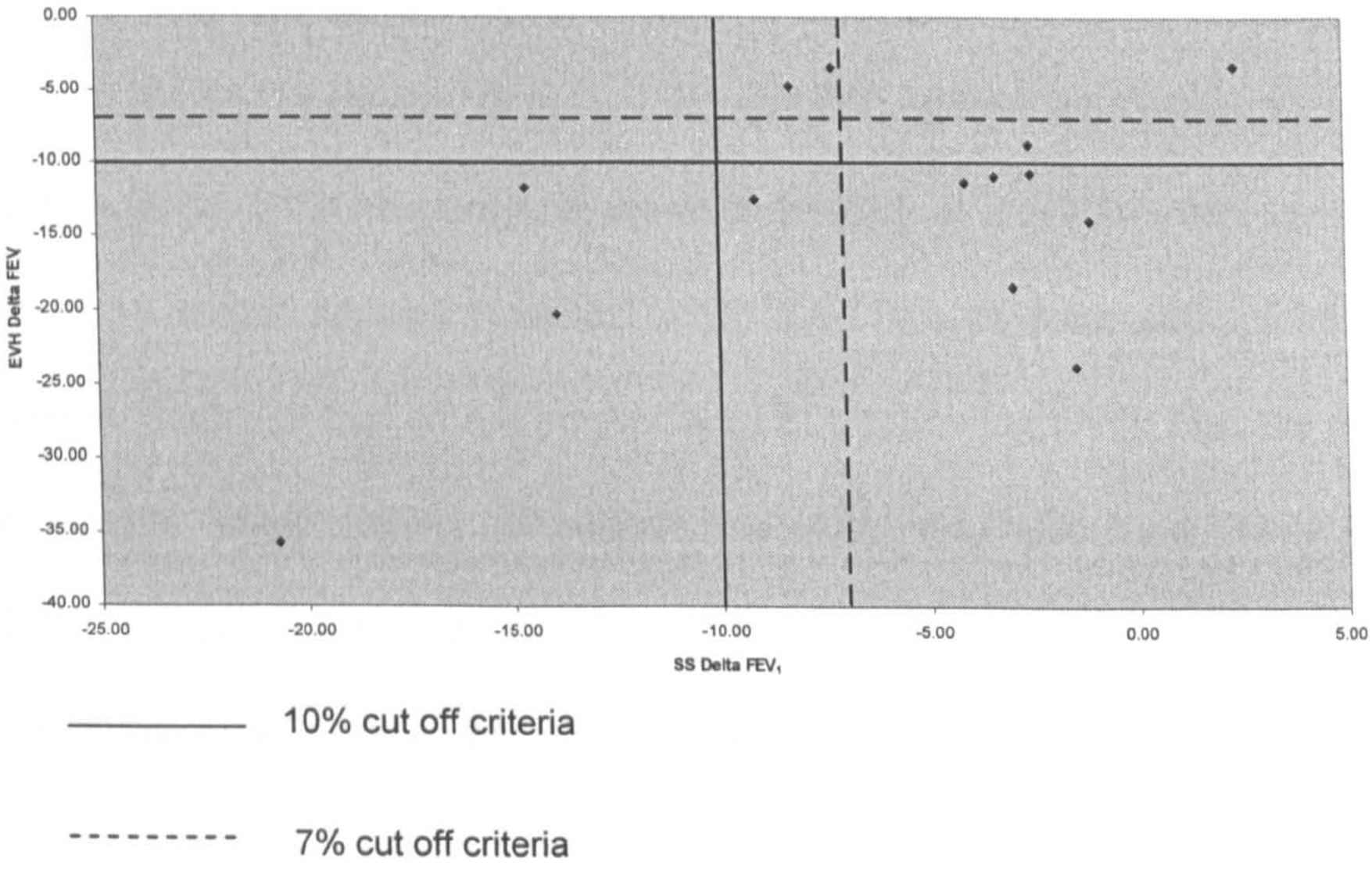

Figure 6.3: SS challenge vs EVH challenge

6.4 Discussion

Data from the present study suggests that screening elite athletes for EIA is warranted. In addition to the 2 athletes who had a previous history of EIA, screening identified 8 athletes, with no previous history of EIA, who presented with significant (>10% fall in FEV_1) bronchial hyperresponsiveness to EVH. This finding concurs with previous studies and chapter 4 that suggest many athletes fail to report and/or recognise symptoms of EIA (Rundell et al., 2001; Bokulic, 2002; Holzer et al., 2004).

Results from the present study demonstrate that the EVH challenge resulted in the greatest number of athletes presenting with bronchial hyperresponsiveness (ΔFEV_1>-10%) commensurate with the diagnoses of EIA. Results from this study are similar to studies that have compared exercise and EVH challenges in winter athletes (Mannix et al., 1999; Rundell et al., 2004) and suggest that the EVH challenge provides a more sensitive diagnosis of EIA in elite winter athletes than any other routinely used, non-pharmacological challenge. In the present study all athletes who presented with EIA did so through the EVH challenge. In contrast, Rundell et al. (2004) demonstrated that 19 out of 38 winter athletes presented with EIA. Two of these athletes had a positive exercise challenge but did not present with EIA following EVH. Had the present study recruited a larger number of athletes the study may also have found that the SS challenge identified athletes who did not respond to EVH. However, it is clear that EVH is a sensitive and specific challenge for the diagnosis of EIA in elite athletes.

The superiority of the EVH challenge is primarily due to the greater degree of control over the two main contributors to the airway response, viz., inspired air water content and minute ventilation. The enhanced control over the condition of the inhaled air and

breathing rate during the EVH challenge allows greater confidence that the airways are being adequately stimulated to trigger bronchoconstriction in susceptible athletes.

In line with the greater control of inspired air water content during the EVH challenge, findings from the present study are more consistent with the hyperosmolarity theory of EIA pathogenesis (Anderson, 1984; Anderson and Daviskas, 2000; Evans et al 2005; Hahn et al 1984; Holzer et al 2002) rather than the airway re-warming theory (Anderson and Daviskas, 2000; Anderson and Holzer, 2002; McFadden et al., 1986). Despite the colder inspired air temperature during the SS challenge (1°C Biathlon, 8°C Speed Skaters) compared with the LB challenge (18°C), only a limited number of athletes (3) presented with EIA following the SS challenge. The EVH challenge, which had the greatest number of positive tests (10 athletes), was conducted with inspired air temperatures (19.1°C) similar to that of the LB challenge, however the relative humidity (RH) of the inspired air (RH<2% H_2O content) was lower than either the LB (RH=c.60% H_2O content) or SS (RH=31-35% H_2O content) challenge. The more provocative nature of dry air inhalation, compared to cold air lends support to the notion that the underlying mechanisms for the development of EIA are not temperature-related.

The lower number of athletes who presented with EIA following SS and LB challenges may be a result of the 10% FEV_1 criterion not being sensitive enough to detect EIA following LB or SS challenge. Work by Helenius et al. (1996; 1998) has suggested that the 10% cut-off criterion for FEV_1 may be insufficiently sensitive to detect EIA in elite athletes and argue that it is not statistically justified. They suggest a fall in FEV_1 of 6.5% as a suitable cut-off criterion for elite runners. Similarly, Rundell et al. (2000) suggest a fall in FEV_1 of 7.1% is a justified value to diagnose EIA in elite athletes.

These studies calculated the FEV_1 cut-off criteria on the basis of the 95th percentile (defined as two standard deviations) of the post-exercise decline in FEV_1 observed in a non-asthmatic population.

In line with Rundell et al. (2000) recommendation, we assessed a reduction in the cut-off criterion for ΔFEV_1 to 7%. This resulted in a further two athletes being classified as positive in response to the SS challenge, and one in response to the LB challenge (see figures 6.1 and 6,2). Thus, a reduction in the criterion fails to improve the sensitivity of the SS and LB challenges to the extent that no false negative responses are observed. Further work is required to establish standardised cut-off criteria for falls in FEV_1 following various challenges. This may reveal that the criterion for exercise challenges should be lower than the criterion ($FEV_1 \geq$-10%) for an EVH challenge.

6.5 Conclusion

The observations in the present study support the role of screening elite athletes for EIA and suggest that EVH is a more sensitive challenge for the detection of EIA in asymptomatic athletes compared with SS and LB challenges. Therefore, if sporting governing bodies were to implement screening programmes to test athletes for EIA, it is recommended that EVH should be the challenge of choice.

Chapter 7

Athletes, Exercise Induced Asthma and Optimal Medication

7.1 Introduction

Exercise-induced asthma (EIA) affects approximately 20% of elite athletes (see chapter 4). Chapters 5 and 6 have demonstrated that a fall in FEV_1 of $\geq$10% following a eucapnic voluntary hyperpnoea (EVH) challenge is a specific and sensitive diagnostic test of EIA in elite athletes. If an athlete presents with EIA following a recognised test it is important that he/she receives optimal management and pharmaceutical treatment. In the absence of efficacious pharmacologic therapy, there may be deteriorations in well-being and performance. At present, few controlled studies examining the efficacy of asthma drugs in elite athletes are available (Helenius et al., 2005).

There are a number of medications that have been reported to attenuate EIA, however, at present, inhaled corticosteroids and inhaled β_2-agonists are recommended as the first line treatment for individuals with asthma by the British Thoracic Society (BTS, 2004). In accordance with the BTS guidelines, inhaled short acting β_2-agonists should be used in the first instance for mild intermittent EIA (step 1). If symptoms are not controlled, inhaled corticosteroids should be used in addition (step 2) and then inhaled long-acting β_2-agonists (step 3) if symptoms are not controlled by the use of both short-acting β_2-agonists and corticosteroids (table 2.4).

Since 1976 it has been accepted that inhaled β_2-agonists are effective in the prevention of EIA (Anderson et al., 1976). Within the elite athlete population the number of

submissions for inhaled β_2-agonists has increased at each Olympic Games since 1984 (IOC-MC 2002). However, Anderson and Brannan (2004) have recently suggested that the long-term use of inhaled β_2-agonists may lead to a worsening of asthma severity. Kalra et al. (1996) and Van Veen et al. (2003) have both reported that only a small dose of inhaled long-acting β_2-agonists can cause the bronchial smooth muscle to become more sensitive to a provocative stimulus. Furthermore, once daily use of long-acting β_2-agonists results in a reduction in the duration of its protective effect upon the airway from bronchoconstriction (Hancox et al., 2002; Simons et al., 1997). Therefore, sole use of β_2-agonist therapy to attenuate EIA should be undertaken with caution, as this treatment does little to attenuate the underlying airway inflammatory and remodelling processes that may occur (Anderson and Brannan, 2004).

Corticosteroids have previously been reported to be associated with a reduction in inflammatory cells in the airway (Schleimer, 1983), as well as an improvement in symptoms, lung function and asthma exacerbation frequency (Dompeling et al., 1993). Therefore, the use of corticosteroids should attenuate the potential airway remodelling processes that may occur within individuals who have EIA. Recent studies have reported that the addition of long-acting inhaled β_2-agonists to corticosteroid therapy leads to better symptomatic asthma control and lower frequency of exacerbations (Shrewsbury et al., 2000; Koopmans et al., 2005; Masoli et al., 2005). However, Aziz et al. (2000) reported that patients preferred the combination therapy, despite the fact that it provided no greater effect on inflammatory markers (exhaled nitric oxide and serum eosinophilic cationic protein) than corticosteroid therapy alone.

Inhaled corticosteroid and long-acting β_2-agonist therapy may attenuate the signs and symptoms of EIA compared to short-acting medication and single medication alone in non-athletes. It remains unclear at present however, which pharmaceutical interventions are optimal for elite athletes with EIA. Accordingly the purpose of the present investigation was to examine the effects of corticosteroid (fluticasone propionate) and long-acting β_2-agonist (salmeterol) therapy in the control of EIA in athletes.

7.2 Methods

Following approval from Harrow Local ethics committee, elite athletes who had a previous positive ($\Delta FEV_1 \geq$-10%) eucapnic voluntary hyperpnoea (EVH) test were approached to take part in the study. Three male and 5 female elite athletes (mean$\pm$SD; age 21.8$\pm$4.0 years; height 171.0$\pm$11.2cm; body mass 66.0$\pm$12.3kg), who had previous diagnosis of EIA, volunteered and provided written informed consent. Athletes came from a range of sports: 4 athletics, 1 slalom canoe, 1 swimming, 1 rowing and 1 short track speeding skating.

Athletes were prescribed the following inhaled pharmaceutical therapies, in a randomised double blind design, for a three week period with a two week washout between each intervention: (a) 200mcg fluticasone propionate (FLU), (b) 50mcg Salmeterol (SAL), (c) 250mcg fluticasone propionate and salmeterol in combination (FXS) or (d) placebo (PLA). Each medication was given to the athlete as a inhaler labelled either A, B, C or D. Neither the athlete nor the researcher knew what medication was being used. At the cessation of the study the athlete discovered what the medications were through consultation with the English Institute of Sport doctor. Athletes using long term therapy (e.g corticosteroids, long acting β_2-agonist) at the

initiation of the study ceased medication two weeks before they began the first 3 week course of test treatment (figure 7.1). Throughout this period and following 18 weeks of the study, athletes were prescribed inhaled salbutamol to use when required. Athletes were also asked to keep a daily diary that included: 1) recording the use of treatment medication (am and pm), 2) number of hours of aerobic training 3) the number of salbutamol inhalations required each day.

A 3 week intervention was thought to be the most suitable time to allow all the medications to reach their optimum protective effect following consultation with English Institute of Sport Doctors and the ethical committee. A two week wash was thought an appropriate time to allow all medication to leave the body before the next medication was started. This time period was suggested by the drug manufactures and deemed acceptable by the ethics committee.

Following each three week period of treatment medication the athlete completed an EVH challenge (Anderson et al., 2001) with maximal voluntary flow volume loops and exhaled nitric oxide (eNO) analysis measured before and 3, 5, 10 and 15 minutes after the EVH challenge (see chapter 3.4 for EVH methods).

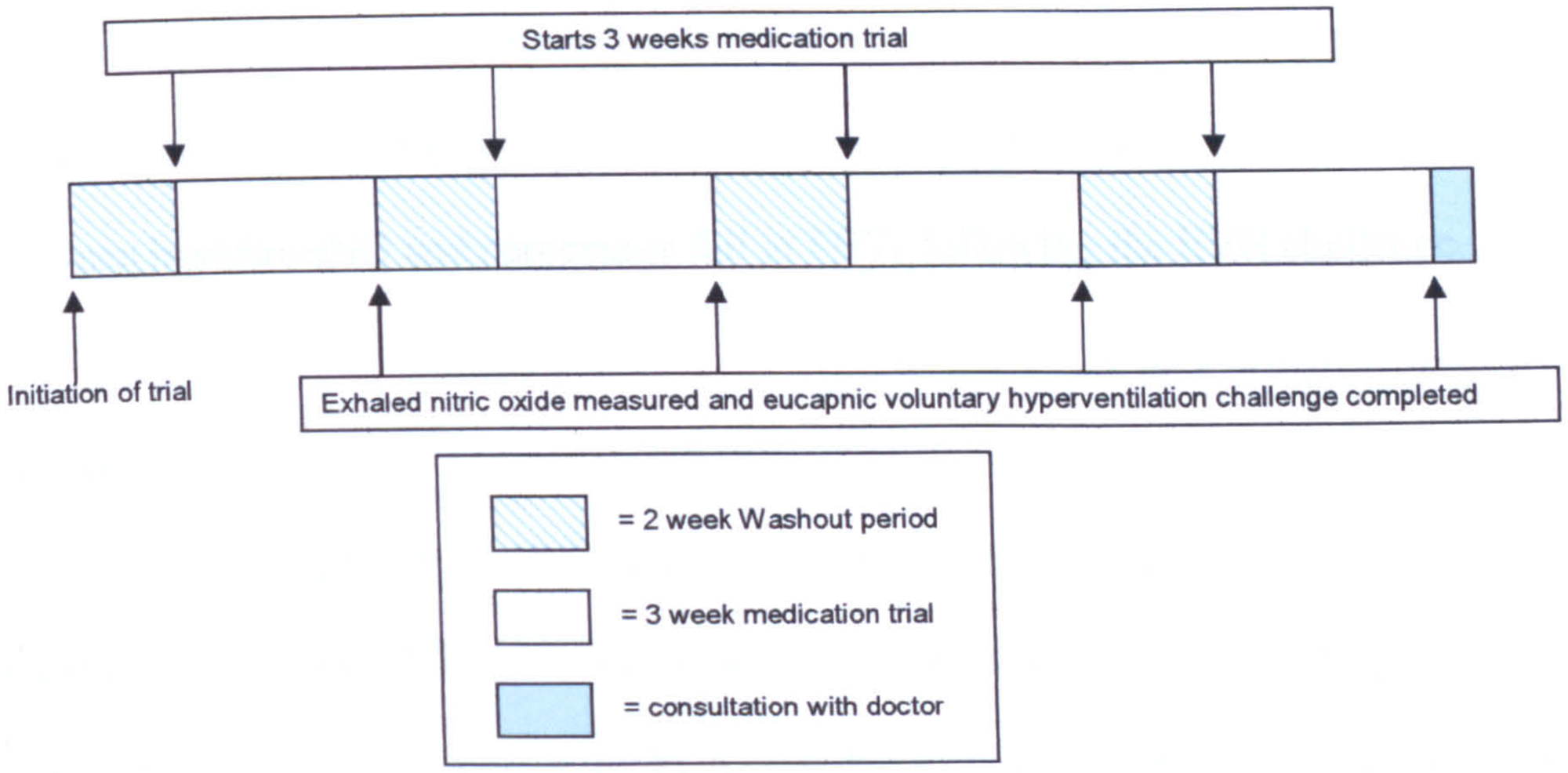

Figure 7.1: Schematic of medication trial

Exhaled Nitric Oxide (eNO) was measured using an online analyser (NOA-280i Nitric Oxide Analyser, NO Analysis software Version 3.21, Sievers Instruments, Boulder) according to American Thoracic Society guidelines (ATS, 1999). The procedure for eNO analysis was: 1) maximal inhalation to total lung capacity and 2) immediate exhalation against a resistance for at least 6 seconds to obtain a NO plateau lasting at least 3 seconds. During exhalation subjects were instructed to monitor a visual computer display to maintain a flow rate of 50 $mL \cdot s^{-1} \pm 10\%$ at a pressure of 16 cmH_2O. Three measurements of eNO were taken at each time point and the mean of the three measurements was recorded. All eNO measurements were taken before spirometry at each time point.

Statistics

Repeated measures ANOVA were used to compare the means of resting FEV_1 and eNO and percent changes in FEV_1 and eNO following the EVH challenge for each treatment. Significance was assumed when $p \leq 0.05$. Mauchly's Test was used to test for the assumption of sphericity. Sphericity was assumed if $p > 0.05$. If sphericity was not

assumed ($p<0.05$) the Greenhouse-Geisser correction factor was applied to assess within subjects effects. A Pearson's correlation was used to investigate the relationship between baseline eNO and percentage fall in FEV_1 following the EVH challenge.

7.3 Results

Six athletes completed all 4 treatments. One athlete was able to complete resting measurements during FXS, but was unable to undertake the EVH challenge; a second athlete was unable to complete the PLA trial due to illness. Both athletes completed all other assessments, however, data from their EVH and eNO measurements were excluded from repeated measures ANOVA. Individual measurements for baseline FEV_1, eNO and percentage change in FEV_1 following EVH challenges are reported in table 7.1. Repeated measures ANOVA revealed no significant difference for the number of salbutamol inhalations taken, or hours of aerobic training across the different treatment periods of the study.

Athlete	Baseline FEV_1 (litres)				Post EVH FEV_1 change from baseline (%)				Baseline eNO (ppb)				Reported Atopy	Medication Prescribed
	FXS	FLU	SAL	PLA	FXS	FLU	SAL	PLA	FXS	FLU	SAL	PLA		
1	4.0	3.5	3.8	3.8	-13	-24	-27	-11	24.9	36.4	89.6	35.8	Yes	FXS
2	3.3	3.0	3.1	3.1	-21	-26	-41	-50	8.1	10.1	28.9	32.1	Yes	FXS
3	4.3	4.1	4.1	4.1	-13	-8	-23	-22	33.4	25.6	38.4	75.7	No	FLU
4	4.1	4.1	4.0	4.0	-2	-2	-5	-8	19.2	19.6	43.9	67.8	No	FLU
5	3.4	3.2	3.3		-7	-5	-7		24.0	28.4	30.0		No	FLU
6	5.9	5.9	6.2	5.7	-12	-5	-6	-9	21.8	19.0	14.8	14.6	No	FLU
7	4.2	4.3	4.3	4.3		-14	-10	-14	21.6	16.9	50.3	77.6	No	SAL
8	3.6	3.4	3.6	3.2	-24	-13	-6	-9	12.8	10.0	9.5	20.2	No	SAL

Table 7.1: Individual responses to Baseline FEV_1, eNO and percent change in FEV_1 following EVH challenge

This table demonstrates the individual responses to each treatment for the following parameters: Baseline FEV_1, Baseline eNO and percentage change in FEV_1 following an EVH challenge. To calculate the percent change in FEV_1 the lowest FEV_1 measured following the EVH challenge was compared to the baseline value. FXS = Fluticasone Propionate and Salmeterol; FLU = Fluticasone Propionate; SAL = Salmeterol; PLA = Placebo. An athlete was considered to have reported atopy if they reported suffering from hay-fever.

Repeated measures ANOVA demonstrated a significant difference (p=0.03) between the means of the total expired air following the EVH challenge after the four treatments (table 7.2). Post hoc Pairwise comparisons demonstrated that the total amount of air expired during the EVH challenge following FXS was significantly greater (p=0.05) than that expired following FLU, SAL and PLA. Repeated measures ANOVA however, did not identify any significant difference in the FEV_1 change (ΔFEV_1) following EVH challenge between the 4 treatments. Repeated measures ANOVA identified a difference between the means of baseline FEV_1 for the 4 treatments (table 7.2) that approached significance (p=0.07), suggesting FXS treatment resulted in greater baseline FEV_1 values compared with FLU and PLA treatments (figure 7.2). The greatest fall in FEV_1 from baseline occurred at 5 minutes post-EVH challenge for all treatments (figure 7.3). The FEV_1 improved at the 10 minute post-EVH measurement, with a similar improvement shown at 15 minute post-EVH measurement. However, FEV_1 did not return to the baseline values. Forced vital capacity measures were similar at baseline and reduced to a similar level following EVH challenge for all treatment groups.

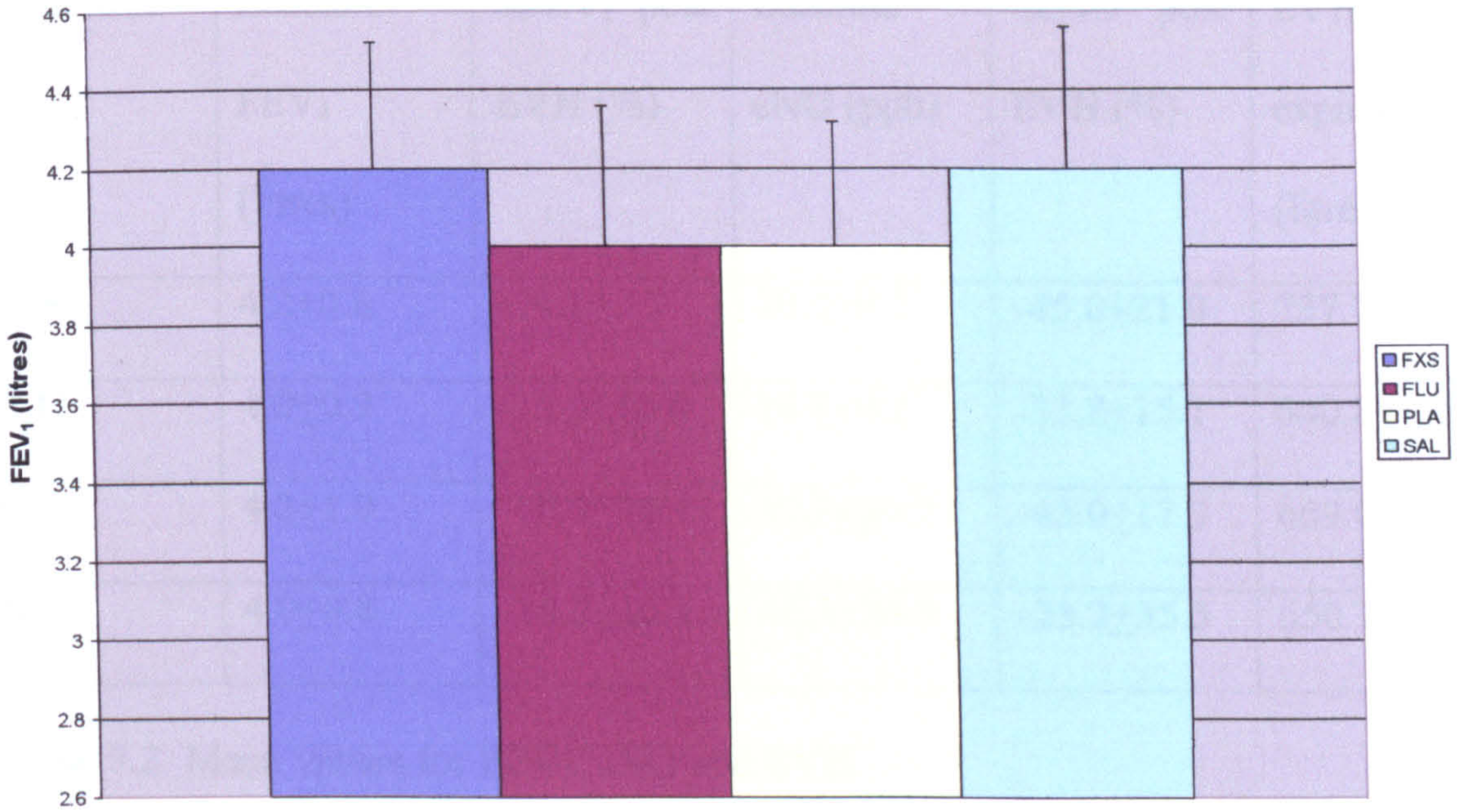

Figure 7.2: Baseline FEV_1

Figure 7.2 shows the means (±SE) values for each treatment. Repeated measures ANOVA identified a difference between the means of baseline FEV_1 for the 4 treatments that approached significance (p=0.07).

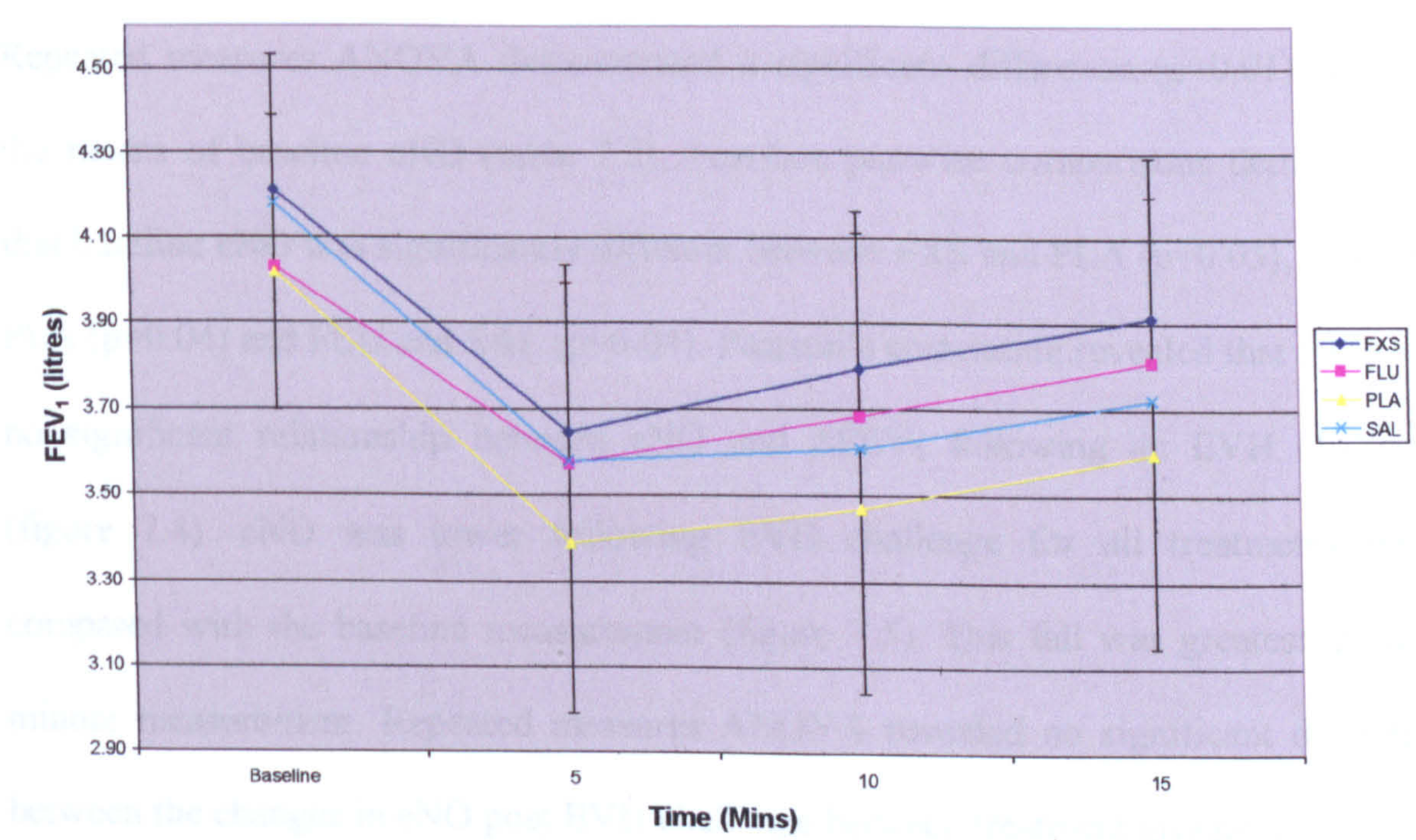

Figure 7.3: FEV_1 before and after EVH Challenge

Figure 7.3 demonstrates the ΔFEV_1 (mean ±SE) at each time point following EVH challenge. Repeated measures ANOVA did not identify any significant difference in the max ΔFEV_1 following EVH challenge between the 4 treatments

Treatment	Baseline FEV_1 (litres)	ΔFEV_1 post EVH (%)	Baseline eNO (ppb)	ΔeNO post EVH (%)	EVH total expired air (litres)
FXS	4.2±0.8	-14.2±7.7	20.3±8.2^{+}	-45.0±21.0	737.7±210.8$^{\$}$
FLU	4.0±0.9	-13.0±10.0	19.7±9.2^{+*}	-33.8±15.1	640.8±138.6
SAL	4.2±1.0	-18.0±16.4	39.3±26.7	-45.0±17.9	669.0±163.2
PLA	4.0±0.8	-18.2±16.4	46.3±26.8	-23.2±35.5	650.7±148.9

Table 7.2: Mean values for FEV_1, eNO and EVH

Value reported mean ± SD
+ = significantly lower than PLA
* = significantly lower than SAL
$ = significantly greater than PLA, SAL and FLU
ΔFEV_1 = max change in Forced Expiratory volume in one second
ΔeNO = max change in exhaled nitric oxide

Repeated measures ANOVA demonstrated a significant difference (p=0.01) between the means of baseline eNO (table 7.2). Post-hoc pairwise comparisons demonstrated that baseline eNO was significantly different between FXS and PLA (p=0.03), FLU and PLA (p=0.04) and FLU and SAL (p=0.04). Pearson's correlation revealed that there was no significant relationship between eNO and ΔFEV_1 following an EVH challenge (figure 7.4). eNO was lower following EVH challenge for all treatments when compared with the baseline measurement (figure 7.5). This fall was greatest at the 5 minute measurement. Repeated measures ANOVA revealed no significant difference between the changes in eNO post EVH challenge between treatment groups.

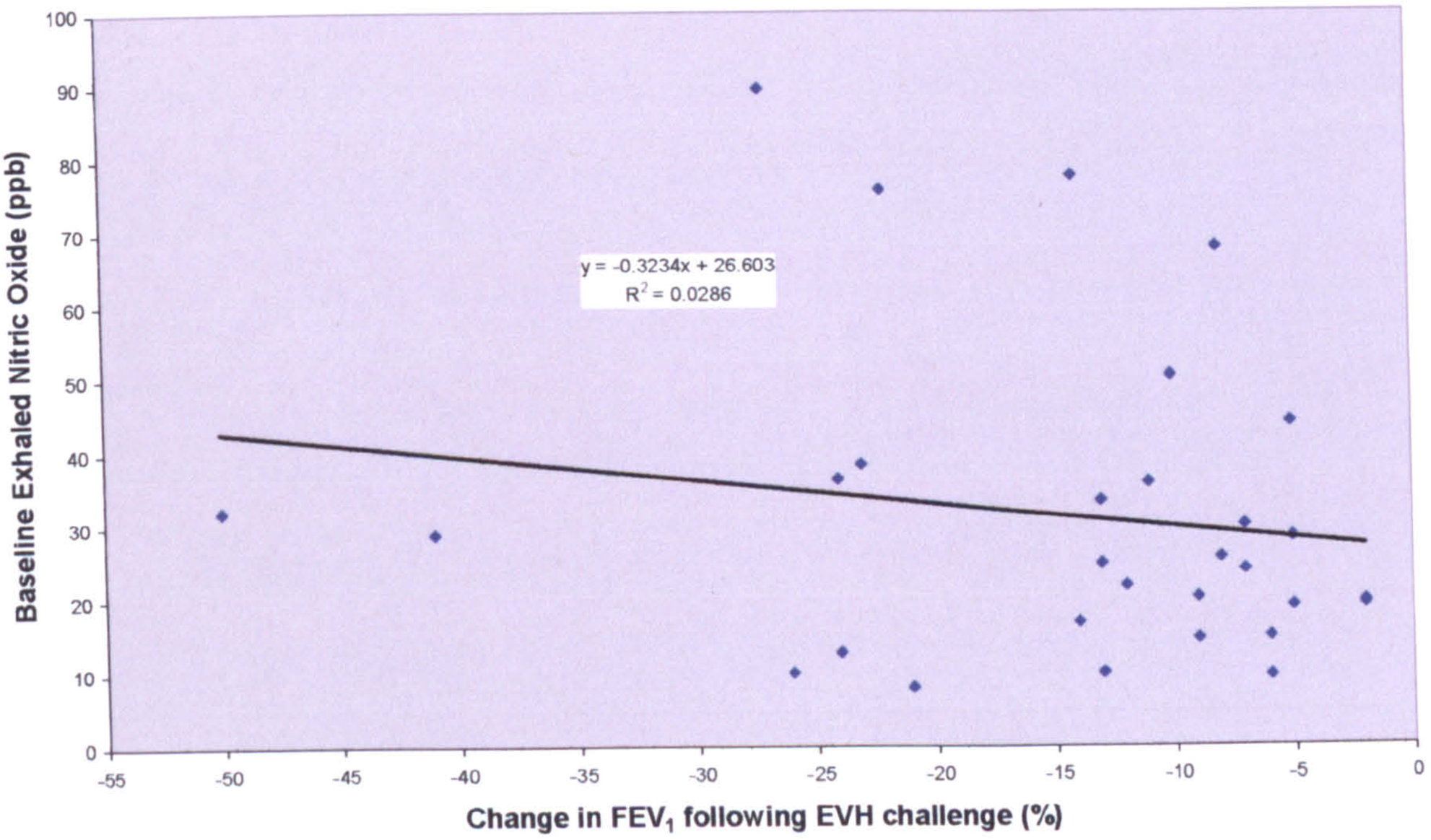

Figure 7.4: Correlation between baseline eNO and change in FEV_1 post EVH challenge

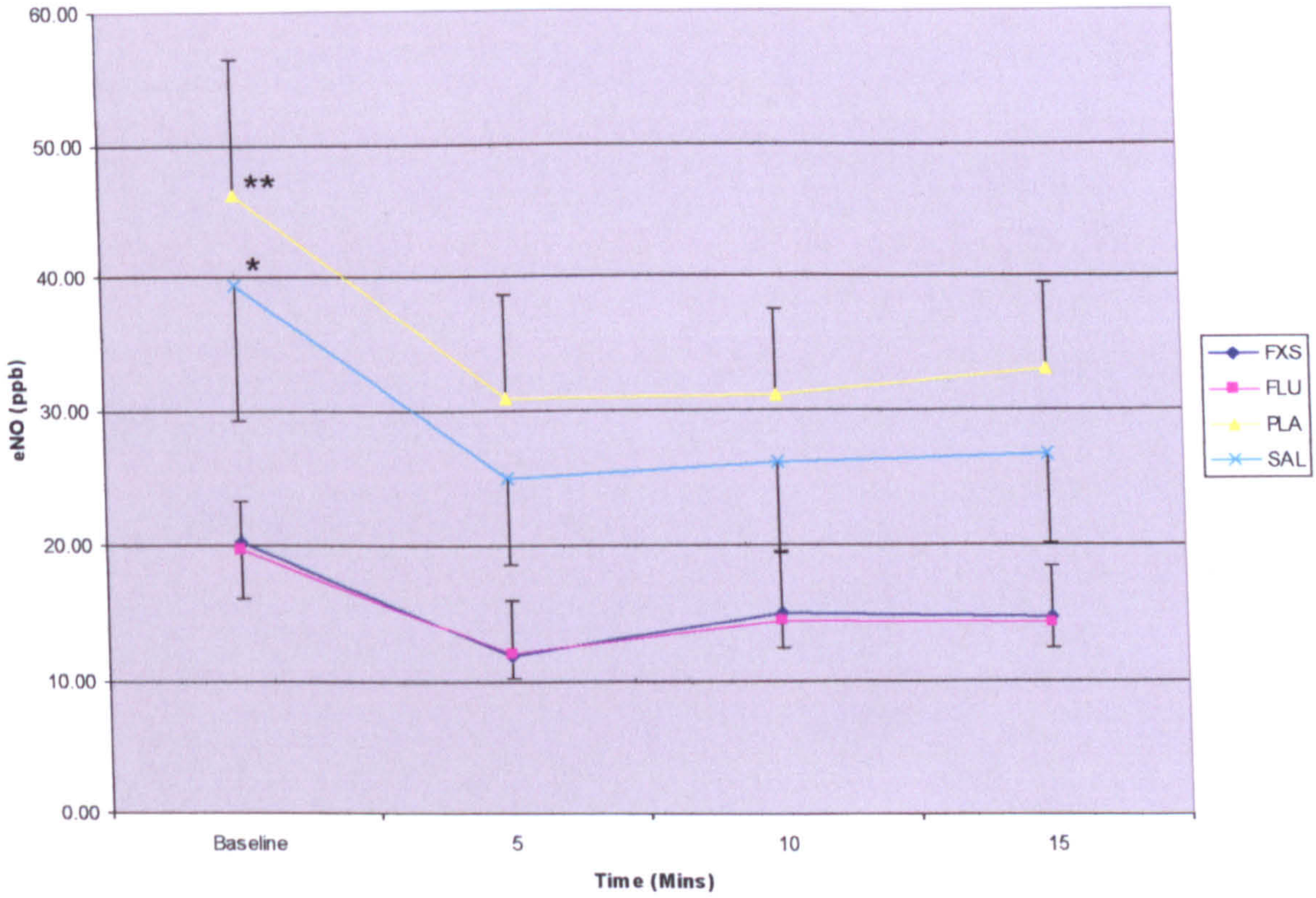

Figure 7.5: eNO Before and After EVH Challenge

*= significantly greater than FLU; **= significantly greater than FLU and FXS

Following the completion of the study each athlete had a consultation with an English Institute of Sport doctor to review the results. Athletes were prescribed ongoing

medication based on the results of the tests and the symptoms athletes reported during each drug trial. Four athletes were prescribed FLU, two athletes were prescribed FXS and two athletes were prescribed SAL (table 7.1).

7.4 Discussion

This study demonstrates that there is heterogeneity of response in elite athletes with EIA to the three medication regimes employed in the present study. The heterogeneity is highlighted by the medications prescribed to the athletes on a long term bases following the 5 month trial (4 Fluticasone Propionate: 2 Salmeterol: 2 Fluticasone Propionate and Salmeterol in combination). The heterogeneity of the responses suggests that the pathogenesis of EIA may vary between individuals. Anderson and Kippelen (2005) suggest that the pathogenesis of bronchoconstriction is associated with several cascades (figure 7.6). Some of these cascades may involve more inflammatory mediators than others. The Anderson and Kippelen (2005) model of EIA pathogenesis, suggests that the individual pathology resulting in bronchoconstriction may vary between individuals with EIA. Therefore, environment, EIA severity, sport and individual physiological profiles should be considered before pharmaceutical intervention to attenuate EIA as opposed to following general population guidelines (BTS, 2004).

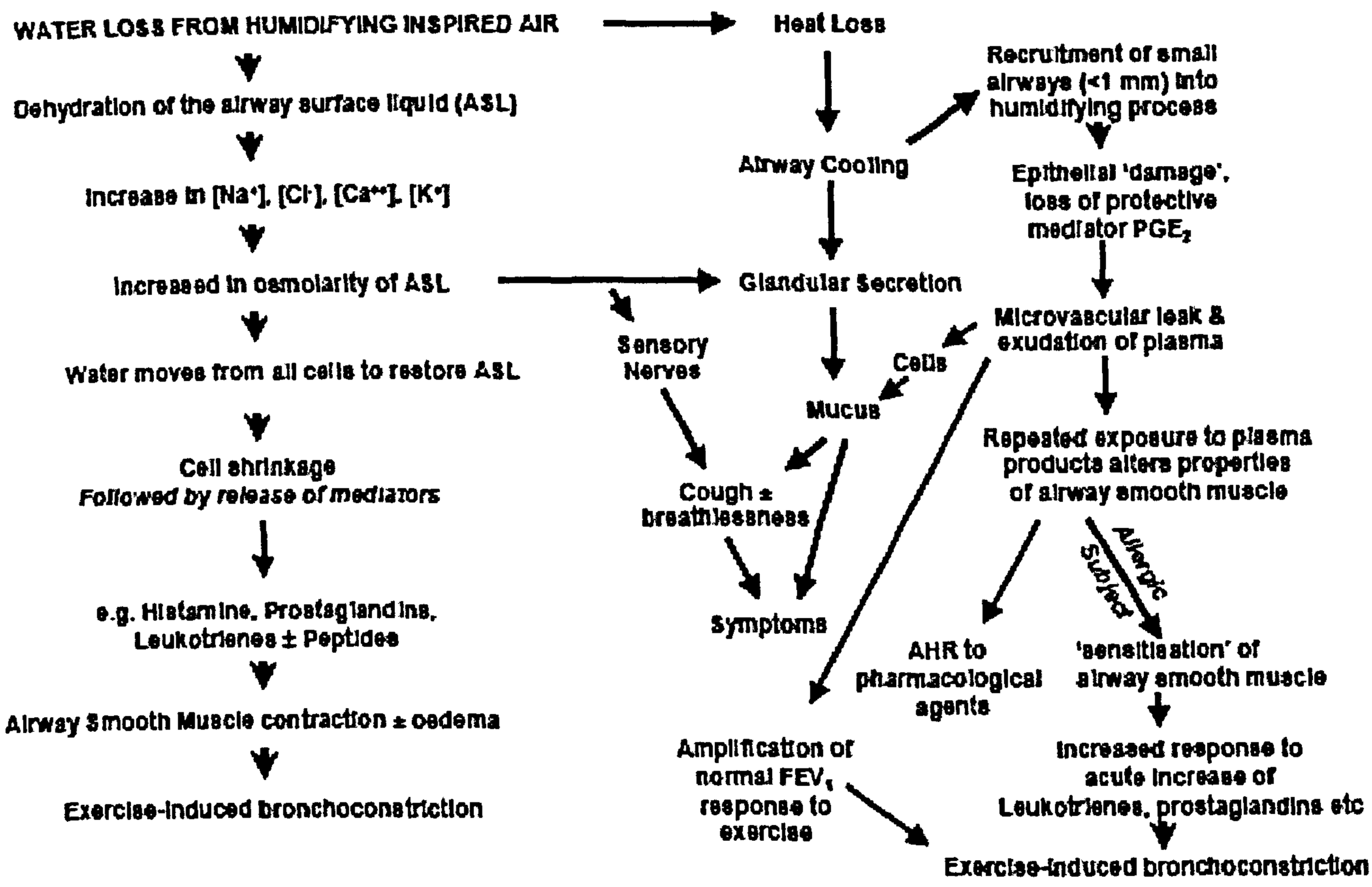

Figure 7.6: Flow-diagram of the pathogenesis of EIA

Flow chart describing the acute events leading to EIA in the classic asthmatic (left) and the events leading to the development of EIA in the athlete (right) (*From Anderson, S. & Kippelen, P. (2005). 'Exercise Induced Bronchoconstriction-Pathogenesis'. Current Asthma and Allergy Reports, vol. 5, pp. 116-122)*

There is obviously a potential for the heterogeneity of response to the medications to be due to inter-individual pathogenic differences, however the observed heterogenity may also be due to the significant difference between the ventilation rates achieved during the EVH challenges. One of the advantages of an EVH challenge is that minute ventilation ($\dot{V}_E$) can be monitored and controlled (Anderson et al., 2001). In the present study the total expired air volume differed between the FXS and other trials. Fluctuations in the ventilation rate can alter the observed bronchoconstriction response (O'Cain et al., 1980). Therefore, the larger volumes of air expired during the FXS EVH challenge may have resulted in greater reductions in FEV_1 following EVH. Thus, the bronchoconstriction observed following the FXS EVH challenge may have been smaller

had the athletes $\dot{V}_E$ during each EVH challenge been similar under all conditions. This may have been achieved by using 85% of maximal minute ventilation (MVV) during exercise rather than calculating 85% of MVV from baseline FEV_1 before each EVH challenge (Spiering et al., 2004). The greater $\dot{V}_E$ observed following FXS trial however, may be a result of improved respiratory function, therefore, resulting in greater $\dot{V}_E$. This would suggest the FXS trial resulted in the greatest observed functional improvements when compared to the other medication trials (FLU, SAL and PLA).

Long-acting β_2-agonist therapy in the form of Salmeterol provided greater protection against EIA in 4 athletes, than the use of corticosteroids alone. Two of these athletes benefited from the sole use of Salmeterol as opposed to using it in combination with corticosteroid. Previous research suggests the addition of long-acting β_2-agonist medication is more effective in attenuating EIA than increasing the dose of corticosteroids (Shrewsbury et al., 2000; Koopmans et al., 2005; Masoli et al., 2005). It was surprising however, to observe that Salmeterol in isolation was more beneficial to some athletes than in combination with corticosteroids, or corticosteroids alone in the present study. The results of this study therefore suggest that BTS (2004) and International Asthma Guidelines (GINA 2002), may need to be adapted to accommodate elite athletes with EIA. These recommendations should be interpreted with caution however, given the spectrum of results observed during the present study.

Further investigations are indicated examining the sole use of β_2-agonists in athletes in whom EIA is not attenuated by corticosteroids alone. As previously discussed however, long-term use of β_2-agonists may result in down regulation of β_2-receptors in the lung (Barnes 1995) and the stimulation of chloride secretion and movement across the

epithelial cells to the airway surface leading to the dehydration of the airway submucosa (Boucher, 1994), thereby increasing EIA severity. Anderson and Brannan (2004) suggest that long-acting β_2-agonists in the form of salmeterol and formoterol should be used intermittently to reduce the potentially deleterious effects described above. It may therefore be useful to investigate other potential therapies that may be more suitable for long-term treatment of EIA, but do not increase asthma severity.

In this study, airway inflammation was monitored using online eNO analysis. eNO has previously been demonstrated to correlate positively with induced sputum eosinophilia (Jatakanon et al 1998) and be greater in asthmatics compared with non-asthmatics (Kharitonov et al., 1995; Persson et al., 1994). Previous studies have demonstrated a reduced eNO following treatment with corticosteroids in patients with asthma (Massaro et al., 1995; Alving et al., 1999; Kharitonov et al., 1994, 1996; Silkoff et al., 2001). The findings in the present study concur with previous studies and demonstrate eNO was significantly lower when athletes were using medications that contained corticosteroids (FXS and FLU) compared with athletes using medications that did not contain corticosteroids (SAL and PLA). This suggests that EIA in elite athletes has an inflammatory component in the pathogenesis that is attenuated by inhaled corticosteroids. In the present study however, athletes 6 and 8 (table 7.1) had lower eNO levels following SAL trial compared with FXS and FLU trials, which highlights the heterogeneity in response to medication and the need to assess individuals physiological markers of airway function.

Reducing the level of inflammation within the airway will reduce the potential for the airway to undergo airway remodelling thereby decreasing asthma severity. Previous

studies have demonstrated a reduced EIA severity when eNO was reduced (Massaro et al., 1995; El Halawani et al., 2003; Deykin et al., 1998, 2003). In contrast, the present study demonstrated no relationship between eNO and the level of bronchoconstriction following EVH challenge. This observation suggests that eNO is a poor predictor of EIA severity in elite athletes. This suggestion however, must be viewed with caution as one of the limitations to this study was the 5 months time period over which it was conducted. Not only did the duration of the study result in potential participants declining to take part, but the trial also ran over different seasons of the year. This inevitably resulted in environmental changes caused by a change in season and it is possible that eNO levels were affected during the pollen season. Aronsson et al. (2005) demonstrated greater levels of eNO in asthmatic individuals during the pollen season than during the 'off season'. Therefore, eNO measurements taken during the pollen season may have been affected and may not be a true representation of efficacy of the medication used at the time of the test. In this study two athletes reported an atopic response during the pollen season. During their 5 months trials each athlete used three out of four treatments were over the months of May, June and July when the pollen levels are typically at their greatest (National Pollen and Aerobiology Unit, 2005). Interestingly, both athletes reporting atopy were subsequently prescribed Fluticasone Propionate and Salmeterol, which suggests that the optimal treatment for atopic athletes with EIA may involve combination therapy. However, although two athletes reported atopic reactions to pollen, no skin prick tests were conducted on any of the participants in this study, therefore future studies should employ skin prick tests to identify all atopic participants. Furthermore, future studies should attempt to avoid running therapeutic trials over the pollen season to eliminate its impact on inflammatory markers in the peripheral airways.

A limitation of this study is the small sample size. The small sample size in the present study is partly due to the duration of the study, as many athletes with EIA declined to participate as they could not commit to a 5 month study. The author recognises that type I and II error can not be ruled out because of the small sample size. Future investigations in this area should increase participation, from elite athletes, by reducing the duration of the study. This may be achieved by reducing the number of medications involved in each study.

A further limitation was that the athletes who participated in the present study came from a variety of sports. Chapter 4 reported the prevalence of asthma in the British 2004 Athens Olympic Squad varied between sports (0-44%). It was suggested that the observed variation in asthma prevalence in chapter 4 was due to the different environments in which each sport took place. Exercising in different environments may result in the main trigger for EIA differing depending on the environment. Athletes' optimal treatment may therefore vary depending on the sporting environment. Future studies may consider recruiting more athletes that come from sports whose environment is similar.

7.5 Conclusion

This study is the first to investigate inhaled corticosteroids and inhaled long-acting β_2-agonists therapy in the control of EIA in elite athletes. Corticosteroids either in combination or in isolation attenuated EIA in 75% of the elite athletes in this study. In contrast to the BTS and international guidelines, a small number of athletes experienced the greatest attenuation of EIA with the sole use of long acting-β_2-agonists. These

results suggest the mechanisms for EIA in elite athletes may differ between individuals, which should be taken into consideration before medication is prescribed. Due to the small sample size and the long duration of this study further investigations into optimal medication for elite athletes should be conducted before findings from this study can be adopted into clinical practise.

Chapter 8

General Discussion

The change in the International Olympic Committee Medical Commission (IOC-MC) asthma criteria in 2001 (IOC-MC, 2002) initiated the research for this thesis. Accordingly the data presented is the first research investigating asthma in elite British athletes. A key finding from this thesis was that 20% of British elite athletes presented with asthma/exercise induced asthma (EIA) following an IOC-MC recognised test. This confirms that the asthma prevalence in elite British athletes is greater than that of the British general population of 8% (Asthma UK, 2001) and supports previous studies suggesting greater asthma prevalence in athletes when compared to the general populations (Voy, 1986; Wilber et al., 2000). Furthermore, the asthma prevalence in elite British athletes is greater than the asthma prevalence rates reported from the United States of America Olympic Teams from the 1996 Atlanta Olympic Games (14%) and 1998 Nagano Winter Olympic Games (17%) (Weiler et al., 1998; Weiler and Ryan, 2000). In a recent report of submissions for the use of inhaled β_2-agonists at the 2004 Athens Olympic Games (Anderson et al., 2005), Great Britain had the second highest number of submissions (54) behind Australia (67) and submitted a greater number than countries including the United States of America (53), France (27) and Germany (22). Anderson et al. (2005) did not report the asthma prevalence within each team (due to submissions via the International Association of Athletics Federation), but it is likely the 20% asthma prevalence rate within the Great Britain squad represented one of the highest asthma prevalence rates at the 2004 Athens Olympic Games.

Between the 2000 Sydney Olympic Games and 2004 Athens Olympic Games the asthma prevalence within the Great British Olympic team remained approximately 20%. This is an interesting result as the IOC-MC expected asthma prevalence to reduce due to the introduction of objective data to identify EIA positive athletes, as studies suggesting symptom based diagnosis were not accurate for EIA diagnosis (Rundell et al., 2001). One explanation for the relatively high asthma prevalence within the Great British Olympic team is that Great Britain submitted the greatest number of EVH challenges (31) to the IOC-MC. Chapter 6 demonstrated that EVH challenges had a greater sensitivity than exercise challenges in the diagnosis of EIA in elite athletes, supporting the work from two earlier studies (Mannix et al., 1996; Rundell et al., 2004). Despite this evidence, many countries predominantly used direct airway challenges (e.g. methocholine) to identify asthmatic athletes for the 2004 Athens Olympic Games (Anderson et al., 2005) and 2002 Salt Lake City winter Olympic Games (Anderson et al., 2003). Direct airway challenges such as methacholine have been shown to have a lower sensitivity and specificity than an EVH challenge (Holzer et al., 2002) and therefore may have led to a lower number of athletes from other countries presenting with EIA, following objective testing using direct airway challenges, when compared with Great British athletes. Further research in this area should use a global multi-centre approach employing similar methods and diagnostic criteria in the diagnosis of EIA. This approach would allow a more representative evaluation of EIA prevalence and identify whether elite Great British athletes do actually have the highest asthma prevalence among international athletes, or whether the difference in prevalence is due to the different methods of EIA diagnosis adopted by different countries.

In addition to the sensitivity and specificity of EVH vs exercise, Chapter 5 demonstrated that a fall in FEV_1 following either an exercise or EVH challenge provided greater sensitivity and specificity in the diagnosis of EIA than measures of mid-expiratory air-flow (FEF_{50}). The fall in FEV_1 required by the IOC-MC however, may not be a justified cut-off point for the diagnosis of EIA in elite athletes. Currently an athlete must present with a fall in FEV_1 of 10% or greater following either an EVH or exercise challenge. Studies focusing specifically on athletic populations suggest that the cut-off criterion following an exercise challenge should be a 7% fall in FEV_1 (Helenius et al., 1996, 1998; Rundell et al., 2000). Lowering the cut-off criterion however, would only serve to increase the number of athletes presenting with EIA, as demonstrated in chapter 6 where the reduced cut-off criterion resulted in a greater number of athletes meeting the positive cut-off point. This increases the potential for false positive diagnosis of EIA. Other studies have demonstrated that the cut-off should be increased to 11% (Elliasson et al., 1992), however work by Hurwitz et al., (1995) suggests a cut-off criterion of a fall in FEV_1 of 10% provides 90% specificity for identifying subjects with asthma. As Helenius et al. (1996; 1998) and Rundell et al. (2000) are the only studies that have previously investigated cut-off criteria specifically in athletes further research is required to justify the IOC-MC criterion of a fall in FEV_1 $\geq$ 10% for the diagnosis of EIA in elite athletes. What may be of greater value in the diagnosis of EIA in elite athletes however, is the evidence of airway reversibility following the inhalation of a β_2-agonist such as salbutamol. Evidence of a marked improvement in airflow following inhalation of salbutamol may provide further evidence of the presence of a pathologically mediated bronchoconstriction. Furthermore, evidence of reversibility may be crucial in an athlete who presents with borderline EIA (ΔFEV_1 =-7-11%) following bronchoprovocation. A significant (e.g.

15%) rise in FEV_1 following inhalation of salbutamol in an athlete with borderline EIA could result in them being confirmed EIA positive, whereas a borderline athlete who did not show reversibility would not be confirmed EIA positive.

The greater prevalence of EIA observed in elite British athletes compared to other nation's elite athletes may be associated with genetic differences. Asthma is known as a "complex" heritable disease. Accordingly, a number of gene candidates contributing to individual susceptibility to EIA have been identified, including: ADAM33, DPP10, PHF11 and GPRA (Yamada and Ymamoto, 2005). The relative roles of these genes in asthma predisposition are unclear. To date, no studies have examined genetic profiles of elite athletes presenting with EIA. Given the similar general population prevalence rates of asthma between Great Britain and other countries the role of genetics in the high prevalence rates observed in elite athletes remains unclear. A global multi-centre research study investigating specific EIA genes within elite athletes would help to clarify the role of genetics in the high prevalence of EIA in elite athletes. Furthermore, the identification of the genes responsible for mild asthma/EIA will assist in the early diagnosis of affected individuals and inform treatment algorithms.

The prevalence of asthma within the British general population is similar to worldwide asthma prevalence, which reduces the potential for the genetic contribution to EIA development to differ between nations (Asthma UK, 2001). The differences in prevalence are more likely due to the variety of methods used to diagnose EIA between nations. In addition, the environment in which individual sports take place may have affected the overall prevalence of EIA within the Great British Olympic Team at the 2004 Athens Olympic Games. Competitors from cycling, rowing and swimming made

up over a third of the 2004 Great British Olympic team. These sports had the greatest absolute and relative asthma prevalence within the 2004 Great British Olympic squad. Cycling, rowing and swimming could be thought of as 'high risk asthma' sports as they are endurance based and require the athlete to train and compete within environments that may be more likely to trigger a bronchoconstriction. For instance, the swimmers are likely to train in a chlorinated pool for at least 2 hours daily and long term exposure to the environment of a chlorinated pool has been shown to increase asthma severity (Fjellbirkedland et al., 1995; Mustchin and Pickering, 1979; Penny, 1983; Zwick et al., 1990; Helenius et al., 1998). Rowing involves training outdoor in the early morning which, during the mornings in the winter months, can result in large quantities of dry cold air being inspired during several hours of training. The majority of the cyclists that made up the British team at the 2004 Olympics were based on the track and therefore spent long hours training and competing in dry, dusty velodromes. In these sports, where athletes have high ventilation rates in 'high risk asthma' environments, there may be a greater potential for airway remodelling. Future screening programmes should target these 'high risk' asthma sports including swimming, rowing and cycling to ensure EIA is treated whilst the severity is still mild to reduce the potential for airway remodelling in athletes competing in these sports. Further research should investigate, whether there is a potential for athletes within these sports to be at a greater risk of airway remodelling than other sports with the same aerobic requirements and examine ways of reducing the environmental load placed on the lungs during training.

The atopic status of an elite athlete with EIA may also have an impact on the potential for airway remodelling and increased EIA severity. Helenius et al. (1998) compared falls in FEV_1 after an exercise challenge between those who suffered from EIA in the

winter and those who suffered during the pollen season. The results demonstrated that more athletes presented with a fall in FEV_1 post exercise in the cold, however, those who demonstrated falls in FEV_1 during the pollen season had larger post exercise changes. These observations suggests that athletes who present with EIA following a bronchoprovocation and have a history of atopy may have a greater risk of airway remodelling and increased EIA severity. Atopy status was not measured in the studies presented in this thesis. Accordingly, future studies examining EIA should investigate the link between atopy and EIA. The benefits of this approach may lead to a differential approach in the treatments of atopic and non-atopic athletes with EIA.

General guidelines for the treatment of EIA suggest that individuals with mild EIA or asthma should be given short-acting inhaled β_2-agonists as first line treatment with corticosteroids given if the symptoms persist (BTS, 2004). These guidelines were constructed for the general population and are not specifically targeted at elite athletes. Chapter 7 is the first study to examine the optimal treatment of elite British athletes with EIA. The results indicate that the BTS guidelines are suitable for half of the athletes included in the study. In contrast, half of the athletes benefited from either combination therapy or sole use of long acting β_2-agonists. These results, suggest that consideration should be given to the therapy offered to elite athletes with EIA rather than following the national general population guidelines. Furthermore, the results from chapter 7 support the use of individual assessment of EIA to optimise medication efficacy. The findings from chapter 7 may lead to a separate treatment algorithm for elite athletes, which may include atopy, genetics and sporting environment. Due to the heterogeneity of response to the different medications used in chapter 7 other forms of therapy that are

not included in the BTS guidelines may be beneficial in the treatment of elite athletes with EIA.

Despite chapter 4 reporting no change in asthma prevalence in the 2004 British Olympic team compared with the 2000 British Olympic team, 20% of the athletes reporting using asthma medication failed to present with EIA following bronchoprovocation challenges. Athletes presenting negative for EIA following a bronchoprovocation challenge but who continued to report breathing difficulty either during or after exercise suffer were thought to suffer from unexplained inappropriate breathlessness (UIB) likely associated with inspiratory stridor and/or hyperventilation.

Inspiratory Stridor (IS) is a condition that is characterised by high-pitched inspiratory noise that is often mistaken for the wheeze of asthma (Brugman and Simons, 1998; Corren and Newman, 1992; Niven et al., 1992; Heiser et al., 1990; Baughman and Loudon, 1989; Kivity et al., 1986; Lakin et al., 1984; Christopher et al., 1983). The presence of IS is associated with vocal cord dysfunction (Brugman and Simons, 1998; Corren and Newman 1992; Niven et al 1992; Heiser et al., 1990; Baughman and Loudon, 1989; Lakin et al., 1984) that can be diagnosed by laryngoscopy. Laryngoscopy however, is very invasive and the patient must be symptomatic, which is problematic if the IS is caused by high intensity exercise, thus, symptom based diagnosis is a more common and practical method.

The prevalence of IS is unknown, however, it has been estimated at 2-3% of the general population with the majority of cases reported in adolescent females (Sullivan et al., 2001; Kenn and Schmitz, 1997). The prevalence in elite athletic populations has been

reported to be 5%; with 53% of IS suffers also presenting with EIA (Rundell and Spiering, 2003). Rundell and Spiering (2003) also reported that it is common for IS to be mis-diagnosed as EIA, reporting 7 out of 19 athletes who were diagnosed with IS had a previous diagnosis of EIA. At the time of data collection for chapter 4 there was no intervention readily available for athletes to attenuate their UIB during training and competition. Future research should consider investigating diagnostic procedures for IS/hyperventilation/hypoventilation in elite athletes that is more practical than laryngoscopy and investigate specific treatments for individuals with IS/hyperventilation/ hypoventilation that may be specific to the individual, sport or elite athletes in general.

8.1 Conclusion

This thesis was the first research to investigate EIA in elite British athletes. The prevalence of asthma within elite British athletes at the 2000 and 2004 Olympic Games was 20%, greater than that of the general population (8%). British elite athletes may have the greatest prevalence of asthma when compared with elite athletes from other nations. This difference may be due to genetics, method of diagnosis or the predominant sports within Great British Olympic team.

Measures of mid-expiratory flow (FEF_{50}) should not be used in the diagnosis of EIA in elite athletes. Our data suggest that a more global measure of maximal expiratory airflow (FEV_1) provides the most sensitive and specific diagnosis of EIA, especially when the severity of the disease is thought to be mild. This would suggest that EIA is a disease that is associated with expiratory flow limitation in the large and small airways of elite athletes.

Elite athletes should be screened for EIA, especially those from 'high risk' asthma sports including swimming, cycling and rowing. Eucapnic voluntary hyperpnoea (EVH) is a more sensitive challenge for the detection of EIA in asymptomatic athletes compared with SS and LB challenges. Therefore, if sporting governing bodies were to implement screening programmes to test athletes for EIA, it is recommended that EVH should be the challenge of choice.

The British Thoracic Society guidelines failed to provide optimal therapy for all athletes and therefore guidelines specific to elite athlete may be beneficial to improve treatment of EIA with in this population. The addition of alternative treatments, including dietary

supplementation, may help reduce symptoms and severity of asthma in elite athletes greater than the sole use of pharmaceutical therapy.

A large number of athletes with a previous diagnosis of asthma failed to present with EIA following a recognised bronchoprovocation challenge. Despite failing to present with EIA following bronchoprovocation these athletes still reported symptoms during exercise. It is possible these athletes suffer from conditions such as vocal cord dysfunction, inspiratory stridor and/or inappropriate hyperventilation. Further research examining the diagnosis of these conditions and optimal treatments is required to assist athletes who fail to present with EIA but report breathing symptoms during exercise.

8.2 Hypotheses – accepted or rejected

1. H_1 The prevalence of asthma in the British Olympic Team will be reduced at the Athens 2004 Summer Olympic Games when compared to the prevalence at the Sydney 2000 Summer Olympic Games associated with the introduction of the IOC-MC requirement for objective evidence of asthma - **rejected**
2. H_1 The addition of FEF_{50} in the diagnosis of EIA will provide a greater sensitivity and specificity - **rejected**
3. H_1 EVH challenges will have a greater sensitivity than exercise challenges in the diagnosis of EIA in elite athletes - **accepted**
4. H_1 Combination therapy in the form of inhaled corticosteroid and long acting β_2-agonist will provide the greatest attenuation to EIA in elite athletes - **rejected**

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APPENDIX 1

IOC-MC guidelines for asthma medication use at Olympic Games

Beta$_2$ adrenoceptor agonists and the Olympic Games in Turin

1. INTRODUCTION

Article 4 of the World Anti-Doping Code refers to the Prohibited List as the international standard. This List, which came into force on 1 January 2005, stipulates that:

All beta-2 agonists including their D- and L- isomers are prohibited. Their use requires a Therapeutic Use Exemption.

As an exception, formoterol, salbutamol, salmeterol and terbutaline, when administered by inhalation to prevent and/or treat asthma and exercise-induced asthma/broncho-constriction require an abbreviated Therapeutic Use exemption.

A simple notification from a respiratory or team physician stating that the athlete has asthma and/or exercise-induced asthma (or exercise-induced bronchoconstriction) WILL NO LONGER BE ACCEPTABLE as evidence for that athlete to inhale a permitted beta$_2$ agonist at the 2006 Olympic Winter Games in Turin.

Athletes who request permission to inhale a permitted beta$_2$ agonist during the Olympic Winter Games in 2006 in Turin will be required to submit test results in support of that athlete having objective evidence of asthma and/or exercise-induced asthma (EIA) or exercise-induced bronchoconstriction (EIB).

Requests must be addressed to the IOC Medical and Scientific Department using the on-line Therapeutic Use Exemption request form.

As for every edition of the Games since 2000, the doping control laboratory will report the presence in urine of any beta$_2$ agonist. For any athlete who has not received an authorisation from the IOC Medical Commission to inhale beta$_2$ agonists, or who has not respected the notifications related to the use of these products, the result of the doping control will be considered positive. The procedures in place for positive doping control cases will then be applied.

For any question related to the on-line form, please contact the IOC Medical and Scientific Department, preferably by e-mail at beta2@olympic.org or by telephone on +41 21 621 6111.

BACKGROUND to the decision to require documented evidence of asthma and/or EIA/EIB:

In May 2001, the IOC (Medical Commission IOC-MC) convened a workshop to examine asthma, beta agonists and the Olympic Games. The workshop concluded that:

- At recent Olympic Games, there had been a large increase in the number of athletes notifying the need to inhale a beta$_2$ agonist
- Some athletes may have been misdiagnosed and did not have asthma and/or exercise induced asthma (EIA) or bronchoconstriction (EIB)
- There is no scientific evidence to confirm that inhaled beta$_2$ agonists enhance performance in doses required to inhibit EIA/EIB
- A skewed distribution of notifications of beta$_2$ agonists by sport was observed with a higher prevalence in endurance sports
- The geographic distribution of notifications of inhaled beta$_2$ agents was markedly skewed but correlated well to the reported prevalence of asthma symptoms in those countries
- There is some evidence that daily use of an inhaled beta$_2$ agonist may result in tolerance to the medication
- Inhaled corticosteroids may be under-used in athletes notifying the use of beta$_2$ agonists
- Eucapnic voluntary hyperpnoea (EVH) was considered to be the optimal laboratory based challenge to confirm that an athlete has EIA/EIB
- Beta$_2$ agonists when administered systemically do have anabolic effects

In October 2001, the IOC-MC appointed an Independent Panel of experts who established the necessary criteria for an athlete to be granted permission to inhale a permitted beta$_2$ agonist at the Olympic Games in Salt Lake City. The results obtained further to the application of these criteria at the Salt Lake City Games have been published, c.f. J Allergy & Clinical Immunology 2003:111:45-50. Due to the success of the application of these criteria, the IOC has decided to use this rule again at the next edition of the Winter Games in Turin.

Recommendation for withholding medications prior to tests
To provide the optimal test circumstances, some medications must be withheld for 8 to 96 hours before the bronchial provocation test. No short-acting bronchodilators, sodium cromoglycate, nedocromil sodium, or ipratropium bromide for 8 hours. No long-acting bronchodilators or antihistamines for 48 hours. No leukotriene antagonists for four days. Steroids should not be inhaled on the day of the test. No caffeine should be taken on the morning of the test. Avoid vigorous exercise for at least four hours prior to the start of the test and avoid any exercise on the day of testing.

b) Exercise challenge in the laboratory or an exercise test in the field
The response to the exercise challenge is considered positive when there is a fall in FEV_1 of 10% or more compared to baseline during the first 30 minutes post exercise.

To maximise the opportunity for a positive test the exercise test should be performed breathing dry air for 8 minutes with the intensity of exercise close to maximal for the last 4 minutes.

Recommendation for withholding medications prior to tests
To provide the optimal test circumstances, some medications must be withheld for 8 to 96 hours before the bronchial provocation test. No short-acting bronchodilators, sodium cromoglycate, nedocromil sodium, or ipratropium bromide for 8 hours. No long-acting bronchodilators or antihistamines for 48 hours. No leukotriene antagonists for four days. Inhaled corticosteroids should not be administered on the day of the test. No caffeine should be taken on the morning of the study. Avoid vigorous exercise for at least four hours prior to the start of the test, and avoid all exercise on the day of testing.

c) Hypertonic aerosol
Hypertonic solution: a test is considered positive when there is a fall in FEV_1 of 15% or more from baseline after a dose of 22.5 ml of 4.5 gm% saline (e.g. 4.5 g NaCl /100 ml water) has been inhaled. The response is usually reported as the dose required to provoke a 15% fall in FEV_1 (PD_{15}) but can also be reported as the maximum fall after the final dose administered.

Recommendation for withholding medications prior to tests
To provide the optimal test circumstances, some medications must be withheld for 8 to 96 hours before the bronchial provocation test.
No short-acting bronchodilators, sodium cromoglycate, nedocromil sodium, or ipratropium bromide for 8 hours. No long-acting bronchodilators or antihistamines for 48 hour. No leukotriene antagonists for 4 days. Inhaled corticosteroids should not be administered on the day of the test. No caffeine should be taken on the morning of the study. Avoid vigorous exercise for at least four hours prior to the beginning of the test, and avoid all exercise on the day of testing.

d) Methacholine test
A test is considered positive if there is a fall in FEV_1 of 20% or more from baseline at a dose less than or equal to 2 micromoles, 400 micrograms (PD_{20}), after inhalation of a solution with a concentration less, or equal to, 4 mg/ml (PC_{20}), or after inhalation of a maximum of 40 breath units **when the subject is not taking inhaled corticosteroids**.

For applicants taking inhaled steroids for at least three months, the PD_{20} should be equal to or less than 6.6 micromoles, 1320 micrograms or PC_{20} equal to or less than 13.2 mg/ml, or inhalation of a maximum of 130 breath units, to be accepted as proof of airway hyperresponsiveness (AHR) (2,7).
It should be noted that a negative response to methacholine does not exclude exercise-induced asthma in an athlete, and in the event of a negative response, an alternative bronchial provocation test is recommended.

If values for PC_{20} or PD_{20} , or breath units during the Methacholine challenge are in access of the thresholds mentioned above, the athlete may undergo an EVH test or an exercise test on site in Turin * prior to the start of the Games.
* Please contact **Dr Carlo GULOTTA**, Pneumologia II - Fisiopatologia Respiratoria, ASO San Luigi, Regione Gonzole, 10, 10043 Orbassano, Torino, Italie, tél. +39 011 9026 332, 372, 733, tél./fax + 39 011 9026 371, portable +39 335 7609 007, c.gulotta@sanluigi.piemonte.it, fpr@sanluigi.piemonte.it.

2. PROCEDURE

The on-line Therapeutic Use Exemption request form for inhaled $beta_2$ agonists for the Games in Turin must reach the IOC Medical and Scientific Department as soon as possible before 31 January 2006.

Requests will be examined by a group of independent experts. The independent panel's decision will be notified by e-mail to the doctor in charge of the request. It will be his/her responsibility to inform the athlete of the status of his/her request. The NOC's chief physician will also be informed in writing of the independent panel's decision.

Any athlete whose request is refused will have the chance to be retested in Turin.
Please contact **Dr Carlo GULOTTA**, Pneumologia II - Fisiopatologia Respiratoria, ASO San Luigi, Regione Gonzole, 10, 10043 Orbassano, Torino, Italie, tél. +39 011 9026 332, 372, 733, tél./fax + 39 011 9026 371, portable +39 335 7609 007, c.gulotta@sanluigi.piemonte.it, fpr@sanluigi.piemonte.it.

These tests may take up to 1 hour and 30 minutes.
The cost of the test in Turin will be €300 and payable by the NOC.
The results of such investigation shall be final.

Athletes having received an authorisation at past editions of the Olympic Games (Salt Lake City or Athens).
For athletes who received the IOC Medical Commission's authorisation to inhale $beta_2$ agonists at the XIX Olympic Winter Games in Salt Lake City in 2002 (or the Games of the XXVIII Olympiad in Athens in 2004), the authorisation will be carried over for the XX Olympic Winter Games in Turin in 2006, with no additional tests needed. However, so that the IOC Medical Commission can clearly identify these athletes, the on-line Therapeutic Use Exemption request form must imperatively be completed.

3. METHODOLOGY

A measure of forced expiratory volume (FEV_1) at rest, as well as changes in FEV_1 in response to an inhaled bronchodilator or further to a bronchial provocation test, are the indispensable elements that must appear on the on-line Therapeutic Use Exemption request form for $beta_2$ agonists (see below for further details on these tests).

Peak Expiratory Flow (PEF) measurements are unacceptable.

In the request form, information must be provided for at least one of the tests below.
Only tests performed **after February 2002** will be taken into consideration by the independent panel.
Spirometry recordings need not be forwarded but must retained and the independent panel reserves the right to request to view them before issuing any approval.

BRONCHODILATOR TEST:
A bronchial reversibility test is considered positive if there is an increase in FEV_1 of 12% or more of the baseline FEV_1 and exceeds 200 ml after administering an inhaled permitted beta2 agonist by inhalation.

Recommendation for withholding medications prior to bronchodilator test
To provide the optimal test circumstances, short acting bronchodilators (e.g. salbutamol, terbutaline, ipratropium bromide) should be withheld for 8 and long acting bronchodilators (salmeterol, formoterol, tiotropium bromide) for 24 hrs or longer.

BRONCHIAL PROVOCATION TESTS:
Various bronchial provocation tests may be used:
a) eucapnic voluntary hyperpnea test
b) exercise challenge in the laboratory or an exercise test in the field
c) Hypertonic aerosol
d) Methacholine test

a) Eucapnic voluntary hyperpnea test
The eucapnic voluntary hyperpnea test is considered positive when a fall in FEV_1 of 10% or more from baseline is recorded after a 6 minutes period of hyperpnea in dry air. To overcome the problem of any post-test respiratory muscle fatigue, the FEV_1 should be recorded three minutes at least after challenge. It would be usual for the reduction sustained over the next five minutes to be consistent with hyperpnea-induced bronchoconstriction.

Important note
The results of bronchial provocation tests using pharmacological agents other than methacholine (e.g. carbachol, histamine or adenosine monophosphate) will not be accepted.

Recommendation for withholding medications prior to tests
To provide the optimal test circumstances, it is recommended that some medications be withheld for 8 to 96 hours before the bronchial provocation test.
No short-acting bronchodilators, sodium cromoglycate, nedocromil sodium, or ipratropium bromide for 8 hours. No long-acting bronchodilators or antihistamines for 48 hours. No leukotriene antagonists for 4 days. Inhaled corticosteroids should not be administered on the day of the test. No caffeine should be taken on the morning of the study. Avoid vigorous exercise for at least four hours prior to the start of the test, and avoid all exercise on the day of testing.

WELL-CONTROLLED ASTHMA with negative response to all the tests
In the case of an athlete with known, but well-controlled, asthma recording a negative result to the bronchial provocation test, but still seeking approval for the use of inhaled beta2-agonists, the following documentation must be included in the file[1] (in addition to negative results obtained in the bronchial provocation test(s) sent electronically): consultations with their physician for treatment of asthma, hospital emergency department attendance or admission for acute exacerbations of asthma or treatment with oral corticosteroids.

Additional information that may assist includes: the age of onset of asthma; detailed description of the athlete's asthma symptoms, both day and night; trigger factors; medication use; past history of atopic disorders and/or childhood asthma; and physical examination, together with results of skin prick test or RAST to document the presence of allergic hypersensitivity.

At the time of the submission of this type of request, please indicate clearly in the "Comments" section underneath the bronchial provocation test(s) with a negative response, that the athlete's asthma is well controlled. Please also inform us that you are sending a file, in order to avoid your request being automatically refused.

Should the athlete wish to submit a second bronchial provocation test result, the opportunity for further testing will be available in Turin. Please contact: **Dr Carlo GULOTTA**, Pneumologia II - Fisiopatologia Respiratoria, ASO San Luigi, Regione Gonzole, 10, 10043 Orbassano, Torino, Italie, tél. +39 011 9026 332, 372, 733, tél./fax + 39 011 9026 371, portable +39 335 7609 007, c.gulotta@sanluigi.piemonte.it, fpr@sanluigi.piemonte.it.

[1]The files must imperatively be sent **by recorded delivery** to the following address: International Olympic Committee, Medical and Scientific Department, Château de Vidy, CH – 1007 Lausanne, Switzerland.

For any further information or assistance, please contact the IOC Medical and Scientific Department, preferably by e-mail at beta2@olympic.org or by telephone on +41 21 621 61 11.

4. BIBLIOGRAPHY

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Smith CM, Anderson SD. Inhalational challenge using hypertonic saline in asthmatic subjects: a comparison with responses to hyperpnoea, methacholine and water. Eur Respir J 1990; 3: 144-51.

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Methacholine test

Sterk PJ, Fabbri LM, Quanjer PH, Cockcroft DW, O'Byrne PM, Anderson SD, et al. Airway responsiveness: Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Eur Respir J 1993; 6:53-83.

Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing - 1999. Am J Respir Crit Care Med 2000; 161:309-29.

Cockcroft DW, Davis BE, Todd DC, Smycniuk AJ. Methacholine challenge: >comparison of two methods. Chest 2005; 125:839-844

APPENDIX 2

Abbreviated Therapeutic Use Exemption Form

Identification of Anti-Doping Organization

(Logo or Name of the ADO)

Appendix 2

Abbreviated
Therapeutic Use Exemptions
ATUE

Please complete all sections in capital letters or typing

beta-2 agonists by inhalation ❑	**glucocorticosteroids by non-systemic routes * ❑**

*** All routes other than orally, rectally, intravenously and intramuscularly. Dermatological glucocorticosteroids do not require any TUE**

1. Athlete Information

Surname: ..... Given Names: .....

Female ❑ Male ❑ Date of Birth (d/m/y): .....

Address: .....

City: ..... Country : ..... Postcode: .....

Tel.: ..... E-mail : .....
(with international code)

Sport: ..... Discipline/Position: .....

International or National Sporting Organization: .....

2. Medical information

Diagnosis: .....

.....

.....

.....

N.B. Any ATUE may be reviewed at any time, by the ADO and/or WADA

STRICTLY CONFIDENTIAL

Prohibited substance(s): ***Generic name***	Dose	Route	Frequency
1.			
2.			
3.			
Intended duration of treatment: (*Please tick appropriate box*)	once only ❑ emergency ❑ or duration (week/month):		

3. Medical practitioner's and athlete's declaration

I certify that the above-mentioned treatment is medically appropriate and that the use of alternative medications not on the Prohibited List would be unsatisfactory for this condition.

Name: .....

Medical Speciality: .....

Address: .....

Tel.: ..... **Fax:** .....

E-mail: .....

Signature of Medical Practitioner: ..... **Date:** .....

I, ... certify that the information under 1. is accurate and that I am requesting approval to use a Substance or Method from the WADA Prohibited List. I authorize the release of personal medical information to the Anti-Doping Organization (ADO) as well as to WADA staff, to the WADA TUEC (Therapeutic Use Exemption Committee) and to other ADO under the provisions of the Code. I understand that if I ever wish to revoke the right of these organizations to obtain my health information on my behalf, I must notify my medical practitioner and my ADO in writing of that fact.

Athlete's signature: ..... **Date:** .....

Parent's/Guardian's signature: ..... **Date:** .....
(if the athlete is a minor or has a disability preventing him/her to sign this form, a parent or guardian shall sign together with or on behalf of the athlete)

Incomplete Applications will be returned and need to be resubmitted.

Please submit the completed form to the ADO and keep a copy for your records.

STRICTLY CONFIDENTIAL

APPENDIX 3

Abstracts presented at International Conferences

Presented at the British Association of Sports and Exercise Science 2004 Annual Conference.

Resting Maximal Voluntary Flow Volume Loops in Elite Athletes: Asthmatics vs Non Asthmatics

The International Olympic Committee has restricted asthma medication for the 2004 Athens Summer Olympic Games. Athletes must produce quantitative evidence of their asthma in order to permit use of their asthma medication. At present there are no published data describing resting lung function in elite athletes, or how resting lung function differs between asthmatic and non-asthmatic elite athletes. The aim of this study was to characterise the maximal flow volume loops of elite athletes with and without asthma.

The study was carried out at the Olympic Medical Institute and at squad training camps around the UK. Ethical approval was obtained from the Harrow Local Research Ethics Committee. Athletes who held either a British Olympic Association Gold or Silver passport were approached to take part in the study. Athletes (males; 171 non asthmatic, 28 asthmatic: females; 137 non asthmatic, 28 asthmatic) volunteered and completed a consent form. All asthmatic athletes were confirmed as such by a positive bronchoprovication test and were instructed not to use asthma medication for up to three days before the testing. Three maximal flow volume loops were obtained using a Spirometer (MicroLab ML3500, Micro Medical, Rochester, UK), which met European Respiratory Society guidelines. The flow volume loop with the best Forced Expiratory Volume in one second (FEV_1) was recorded. One-Way ANOVA was carried out to compare the means between asthmatics and non-asthmatics in males and females.

The assumption of homogeneity of variance was met ($P>0.05$) for all ANOVA. In males and females age, height and weight were not significantly different ($P>0.05$) between asthmatic and non-asthmatic groups. In males, all maximal flow volume loop measurements were significantly greater ($P<0.05$) in non-asthmatics than in asthmatics (See Table 1). However, in females only Forced Expiratory Flow at 50% of vital capacity (FEF_{50}) and percent of predicted FEF_{50} (ECCS predicted values) were significantly greater ($P<0.05$) in non-asthmatics than in asthmatics (See Table 1)

Table 1. Maximal lung function parameters for male and female asthmatic and non-asthmatic elite athletes (mean±S). NA = non-asthmatic; A = asthmatic; % Predicted = percentage of predicted normal value (ECCS predicted values)

Sex	Group	FEV_1 (l)	% Predicted FEV_1 (%)	FEF_{50} ($l.s^{-1}$)	% Predicted FEF_{50} (%)	FEV_1/FVC (%)
Male	NA	4.73±0.82	105.98±12.43	5.21±1.35	93.15±23.69	83.66±7.05
	A	4.14±0.74	94.82±12.52	3.88±0.97	69.26±16.11	77.01±6.5
Female	NA	3.53±0.63	105.78±13.84	4.37±1.00	94.84±21.42	87.21±7.67
	A	3.50±0.49	104.30±11.02	3.67±0.88	79.53±14.66	86.05±7.06

The results from this study demonstrate that at rest the maximal voluntary flow volume of an asthmatic elite athlete is lower than that of a non-asthmatic elite athlete. This difference is more pronounced in males than in females. The study also highlights the need for athletes to be tested for asthma through bronchoprovication and bronchodilator challenges, as at rest elite asthmatic individuals have FEV_1 values that appear normal (FEV_1 > 90% predicted).

Presented at the American Thoracic 2005 Annual Conference

Fall in FEF_{50} ($l.s^{-1}$) is a more sensitive indicator of bronchial constriction than FEV_1 (l) of PEFR ($l.s^{-1}$) following eucapnic voluntary hyperventilation (EVH)

The IOC criterion to diagnose EIA is a 10% fall in FEV_1 following an EVH challenge. We have shown that FEF_{50} is a more sensitive indicator of bronchoconstriction than any other spirometry measure.

One hundred and fifteen elite athletes, 59 asthmatic (who met IOC criteria), 56 non-asthmatics, underwent an EVH challenge requiring each athlete to hyperventilate at 30 x FEV_1 for 6 minutes (Anderson et al. 2001). Maximal voluntary expiratory flow volume measurements were taken before and 5, 10 and 15 minutes after EVH. A one-way analysis of variance was used to compare means at baseline and following bronchoprovication.

FEF_{50} was the only measurement that was significantly ($P<0.05$) different at baseline between the asthmatic group and the non-asthmatic group, which was maintained following scaling for FVC. FEF_{50} and ISO_{50} fell significantly ($P<0.05$) greater than FEV_1 following the EVH challenge (Table 1).

Table 1. Spirometry measurements before and after EVH challenge in asthmatic (A) and non-asthmatic (NA) elite athletes

	FEV_1 (litres)		PEFR ($l.s^{-1}$)		FEF_{50} ($l.s^{-1}$)		ISO_{50} (FEF_{50}/FVC)	
	A	NA	A	NA	A	NA	A	NA
Pre	3.9	4.09	8.84	9.18	3.86*	4.79	0.79*	1.02
Post	3.07*	3.9	6.81*	8.66	2.39*	4.42	0.53*	0.97

** = Value is significantly ($P<0.05$) lower in the A group.*

In conclusion, FEF_{50} has been shown to be the only spirometry measurement that distinguishes elite EIA athletes at rest from non-asthmatics. Furthermore, FEF_{50} shows a larger fall than FEV_1 following bronchoprovication challenge in EIA positive athletes even after accounting for changes in FVC. Therefore FEF_{50} maybe a more sensitive measure for diagnosing EIA at rest and following an EVH challenge.

Presented at the American College of Sports Medicine 2005 Annual Conference

Impact of the IOC-MC change in asthma diagnosis – A British Perspective

Introduction: Since 2001 the International Olympic Committee-Medical Commission (IOC-MC) has required athletes, who suffer from asthma, to provide evidence of their condition to use inhaled β_2-Agonists. The purpose of this study was to compare the prevalence of asthma at the 2000 and 2004 Olympic Games in the Great British Olympic team (Team GB).

Method: Following local ethics committee approval, athletes (165 males, 106 females) from 2004 Team GB volunteered and signed informed consent. An athlete was confirmed asthmatic if they had a positive bronchoprovication or bronchodilator test recognised by the IOC-MC. Pre-Olympic medical forms from the 2000 Team GB were examined to discover the prevalence of asthma at the 2000 Olympic Games.

	2000			2004		
	No.	No. Asthmatic	% Asthmatic	No.	No. Asthmatic	% Asthmatic
Male	152	29	19.08	165	34	20.6
Female	122	29	23.77	106	22	20.8
Overall	274	58	21.17	271	56	20.7

Results: The asthma prevalence of Team GB is reported in *table 1.*

Table 1: Team GB asthma prevalence at the 2000 and 2004 Olympics

13 out of 62 (21.0%) athletes with a previous diagnosis of asthma tested negative. A further 7 athletes with no previous diagnosis of asthma tested positive. Swimming (41% vs 44%) and cycling (44% vs 39%) had the highest prevalence of asthma at both 2000 and 2004.

Conclusion: The IOC-MC requirement that asthmatic athletes must submit documented evidence of asthma has highlighted that 19.35% of athlete's previously diagnosed asthmatic where unable to provide positive evidence of asthma. Despite this the overall asthma prevalence of Team GB remained unchanged between 2000 and 2004. The more rigorous procedure used in 2004 also provided a number of athletes who tested positive for asthma that had no previous history, symptoms or diagnosis of asthma. It is recommended that all Elite athletes should be screened for asthma regardless of previous history, symptoms or diagnosis of asthma.

Presented at the British Association for Sports and Exercise Science 2005 Annual Conference

Screening elite winter athletes for exercise-induced asthma: a comparison of three challenge methods

Exercise-induced asthma (EIA) is defined as an acute transient narrowing of the airways that occurs following exercise. The reported prevalence of EIA with in elite winter athletes has ranged from 9% to 50% (Wilber, R. *et al.*2000: *Medicine and Science in Sport and Exercise*, **32**, 732-737). At present there is no 'gold standard' test for EIA, but the International Olympic Committee accepts the results of a number of different challenges, including exercise, eucapnic voluntary hyperventilation (EVH), and inhalation of hypertonic substances. In the case of the exercise and EVH, they stipulate a minimum requirement for changes in forced expiratory volume in 1 sec (ΔFEV_1) of 10%. The purpose of this study was to compare the response of elite winter athletes to eucapnic voluntary hyperventilation (EVH) and two exercise challenges (laboratory-based [LB] and sport-specific [SS]).

Following ethical approval from Harrow Local Research Ethics committee, 14 athletes (mean ±SD; age 22.6±5.7years, height 177.2±7.0cm, weight 68.9±16.9kg) from the British Short-track Speed Skating (n=10) and Biathlon (n=4) teams volunteered and provided written informed consent. Each athlete completed an LB challenge, a SS challenge, and an EVH challenge in a random order. The LB challenge required the athlete to run continuously on a treadmill for 8 min (Temperature 18°C, Humidity 40%); during the last 4 min their heart rate (HR) was above 85% HR_{max}. The SS for the speed skaters involved skating for 6 min at race pace on the ice-rink (Temperature 8°C, Humidity 35%). The SS challenge for the biathletes involved a 20 minutes race in Finland (Temperature. 1°C, Humidity 34%). The EVH challenge was conducted in the laboratory (Temperature 18°C, Humidity 40%) and required each athlete to hyperventilate for 6 min (30 x baseline FEV_1) breathing a gas mix consisting of 5% CO_2, 21% O_2, 74% N_2. Spirometry was measured before and at 3, 5, 10 and 15 minutes after stopping each challenge. A fall ΔFEV_1 of 10% from the baseline measurements was deemed positive for EIA. Repeated measures ANOVA were used to compare the ΔFEV_1 for each challenge. A P value of ≤ 0.05 was regarded as significant.

All 14 athletes completed each challenge. Two athletes had a previous history of asthma. Ten of the 14 athletes (including the two athletes with a previous history) had a positive test to at least one of the challenges. Ten athletes had a positive response to EVH (71%); of these, only 3 (21%) also had a positive response to the SS challenge. No athletes had a positive test to the LB challenge. The ΔFEV_1 following EVH was significantly greater ($P \leq 0.05$) than the ΔFEV_1 for either the LB or SS challenge (see table 1).

Table 1 – ΔFEV_1 % changes for each different challenge (Mean ±SD)

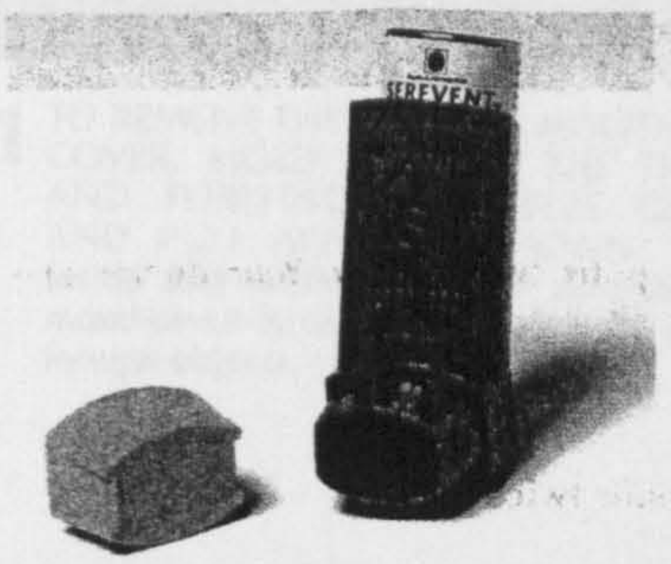
	LB	SS	EVH
Positive EIA ΔFEV_1 % (n=10)	-3.0±3.8	-7.4±6.8	-16.9±8.0**
Negative EIA ΔFEV_1 % (n=4)	-1.1±1.0	-3.9±4.9	-5.1±2.5

**= Significant change in ΔFEV_1 ($P \leq 0.05$)

Our results suggest that the EVH challenge is more sensitive than an exercise challenge to detect EIA in elite winter athletes. The requirement of 10% fall in ΔFEV_1 following an exercise challenge may not be sensitive enough to detect all EIA-positive athletes. Eight out of the 12 (66%) elite winter athletes tested had no previous history of EIA, but had a positive test EVH. An EVH challenge may therefore be considered the most suitable challenge to use when screening athletic populations for EIA.

APENDIX 4

Information Regarding Fluticasone, Propionate and Salmeterol



ALLEN & HANBURYS

Serevent™ Inhaler

salmeterol xinafoate

Patient Information Leaflet for Serevent Inhaler

Your doctor has decided to prescribe Serevent Inhaler as part of your treatment.

This leaflet tells you about Serevent Inhaler and how to use it. Please read it carefully before using your inhaler and keep it until you have finished the medicine.

WHAT IS SEREVENT INHALER?

Serevent Inhaler delivers your medicine as an aerosol spray for you to inhale directly into your lungs where it is needed. Each puff provides 25 micrograms of the active ingredient salmeterol (as salmeterol xinafoate). It also contains the propellants trichlorofluoromethane and dichlorodifluoromethane, and soya lecithin which helps to dissolve the active ingredient. Each canister contains 120 puffs.

To help identify Serevent Inhaler, there is an embossed letter S on the plastic case. There is also a special dimpled 'touch pad' area to distinguish the 'protector' inhalers from 'preventer' or 'reliever' inhalers which have different touch pads.

WHO MAKES YOUR MEDICINE?

Serevent Inhaler is made by Glaxo Wellcome Production, Evreux, France. The product licence is held by Allen & Hanburys, Stockley Park, Middlesex, UB11 1BT.

HOW YOUR MEDICINE WORKS

Salmeterol xinafoate is one of a group of medicines called bronchodilators. It relaxes the muscles in the walls of the small air passages in the lungs. This helps to open up the airways and makes it easier for air to get in and out of the lungs. The effects of salmeterol xinafoate usually last for at least twelve hours. When it is taken regularly, it helps the small air passages to STAY OPEN. This is why salmeterol xinafoate is called a 'protector'.

USES

Serevent Inhaler is used to help breathing problems in asthma and other chest illnesses such as, in adults, Chronic Obstructive Pulmonary Disease (COPD).

If you have asthma you should take your Serevent at the same time as your inhaled corticosteroid and not on its own. If you are not taking this second medication or if you are unsure, ask your doctor.

Serevent Inhaler should NOT be used as a 'reliever' for a sudden attack of wheeze or breathlessness. If you get a sudden attack of wheezing or breathlessness, you should inhale from a quick-acting 'reliever' inhaler. If you feel you are getting breathless or wheezy more often than normal, you should go to see your doctor.

MAKE SURE THAT THIS MEDICINE IS SUITABLE FOR YOU

TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE

* if you are pregnant (or intending to become pregnant),
* if you are breast-feeding a baby,
* if you have ever had to stop taking this or another medicine for this illness because you were allergic to it or it caused problems,
* if you are allergic to soya or related food products such as soya beans,
* if you are allergic to lecithin,
* if you are having treatment for a thyroid condition,
* if you are having treatment for high blood pressure,
* if you have an irregular heart beat/rhythm, including a very fast pulse,
* if you are taking any medicines to control an irregular heart beat/rhythm, including a very fast pulse.

Sometimes this medicine may not be suitable and your doctor may want to give you something different. Make sure that your doctor knows what other medicines you are taking (e.g. other inhalers, treatment to reduce fluid, any other kind of bronchodilator tablets, steroid tablets), including any you have bought from the chemist. Remember to take these medicines with you if you have to go into hospital.

TAKING YOUR MEDICINE

* Serevent Inhaler produces a fine mist which you must inhale into your lungs. Make sure that you know how to use the inhaler properly. The instructions are given later in this leaflet.

HOW TO USE YOUR INHALER

1 TO REMOVE THE SNAP-ON MOUTHPIECE COVER, HOLD BETWEEN THE THUMB AND FOREFINGER, SQUEEZE GENTLY AND PULL APART AS SHOWN. Check inside and outside to make sure that the mouthpiece is clean and that there are no foreign objects.

TESTING YOUR INHALER

If your inhaler is new or if it has not been used for a week or more, shake it well and release one puff into the air to make sure that it works.

2 Shake the inhaler before use.

3 Hold the inhaler upright as shown above with your thumb on the base below the mouthpiece. Breathe out as far as is comfortable and then.....

4 place the mouthpiece in your mouth between your teeth and close your lips around it but do not bite it.

5 Just after starting to breathe in through your mouth, press down on the top of the inhaler to release a puff while still breathing in steadily and deeply.

6 Hold your breath, take the inhaler from your mouth and your finger from the top of the inhaler. Continue holding your breath for a few seconds or as long as is comfortable.

7 If you are to take another puff, keep the inhaler upright and wait about half a minute before repeating steps 2 to 6.

8 After use, always replace the mouthpiece cover to keep out dust and fluff. REPLACE FIRMLY AND SNAP INTO POSITION.

IMPORTANT

Do not rush stages 3, 4 and 5.

It is important that you start to breathe in as slowly as possible just before operating your inhaler. Practise in front of a mirror for the first few times. If you see 'mist' coming from the top of the inhaler or the sides of your mouth, you should start again from Stage 2.

Some people find it difficult to release a puff of medicine just after they start to breathe in. The Volumatic™ large-volume spacer device helps to overcome this problem. Your doctor, nurse or pharmacist will be able to advise you about this.

Young children may need help and their parents may need to operate the inhaler for them. Encourage the child to breathe out and operate the inhaler just after the child starts to breathe in (see picture 5). Practise the technique together.

Older children or people with weak hands may find it easier to hold the inhaler with both hands as shown. Put the two forefingers on top of the inhaler and both thumbs on the bottom below the mouthpiece. If this does not help, a special device called a Haleraid™ may

DOSE

The usual starting dose is:

Adults

1. **For asthma and other chest illnesses: 2 puffs twice a day. Your doctor may increase this to 4 puffs twice a day.**
2. **For COPD: 2 puffs twice a day.**

Children aged 4 and over:

1. **For asthma and other chest illnesses: 2 puffs twice a day.**
2. **For COPD: Not appropriate.**

Serevent Inhaler is not recommended for children under 4.

* It is very important that you use your Serevent Inhaler every day, twice a day, in the morning and again in the evening. This should help to keep you free of symptoms throughout the day and night.
* YOU MUST NOT inhale more puffs or use your inhaler more often than the doctor told you to.
* When you start using Serevent Inhaler, it is important to continue using any other asthma medication, such as inhaled steroids. Continue in the same way as before, unless the doctor tells you otherwise, EVEN IF YOU FEEL MUCH BETTER.
* DO NOT USE THIS MEDICINE TO TREAT A SUDDEN ATTACK OF BREATHLESSNESS. You should use a quick-acting 'reliever' inhaler for this purpose. If you have more than one type of inhaler, be careful not to confuse them. If you are not sure about this, check with the doctor.

IF YOU MISS A DOSE

If you forget to take a dose, do not worry. Inhale a dose when you remember BUT if it is near the time for the next dose, wait until this is due. Then go on as before.

DO NOT TAKE A DOUBLE DOSE.

IF YOU TAKE TOO MUCH

It is important to keep to the dose on the pharmacist's label. If you accidentally take a LARGER DOSE THAN RECOMMENDED, you may notice that your heart is beating faster than usual and that you feel shaky. You may also have a headache. The potassium levels in your blood may be reduced. Tell your doctor as soon as possible.

AFTER TAKING YOUR MEDICINE

* IF YOUR BREATHING OR WHEEZING GETS WORSE STRAIGHT AFTER USING YOUR INHALER, STOP USING IT IMMEDIATELY AND TELL YOUR DOCTOR AS SOON AS POSSIBLE.
* If the relief of wheezing or chest tightness is not as good as usual or does not last for as long as usual, tell your doctor as soon as possible. It may be that your chest condition is getting worse and you may need to start or increase using an inhaled steroid.

SIDE EFFECTS

Most people do not have any problems when taking this medicine.

* Some people may be allergic to this medicine. If you develop a rash or swelling (usually of the face, mouth or throat), stop using your Serevent Inhaler and tell your doctor straightaway.
* Some people may occasionally feel a bit shaky or have a headache.
* Some people who are unusually sensitive may notice that their heart is beating faster than usual. This awareness of their heart beating is called palpitations, is normally harmless, and usually passes off as treatment continues. Some might notice that their heartbeat becomes uneven or their heart gives an extra beat. Tell your doctor but do not stop using this medicine unless told to do so.
* There have been occasional reports of muscle cramps, aching joints, chest pain, nausea (feeling of sickness), dizziness, nervousness, insomnia (difficulty in sleeping) and mouth and throat irritation.
* Very rarely, Serevent Inhaler can affect the salt balance of the body.

If you feel unwell or notice anything unusual which you don't understand, tell your doctor as soon as possible.

STORING YOUR MEDICINE

* Keep your inhaler in a safe place WHERE CHILDREN CANNOT REACH IT.
* Do not store the inhaler above 30°C.
* If the inhaler gets very cold, take the metal canister out of the plastic case and warm it IN YOUR HANDS for a few minutes before use. NEVER use anything else to warm it up.
* WARNING. The metal canister is pressurised. Do not puncture, break or burn it even when you think it is empty.
* Do not use after the date shown as 'EXP' on the carton and label.
* If you are told to stop taking this medicine, RETURN ANY SEREVENT INHALERS TO YOUR PHARMACIST to be destroyed.

CLEANING

Your inhaler should be cleaned at least once a week.

1. Pull the metal canister out of the plastic case of the inhaler and remove the mouthpiece cover.
2. Rinse the plastic case and the mouthpiece cover in warm water. A mild detergent or a solution of the type used to clean babies feeding bottles may be added to the water (your pharmacist will advise you). Then rinse thoroughly with clean water before drying. Do not put the metal canister into water.
3. Leave to dry in a warm place. Avoid excessive heat.
4. Replace the canister and mouthpiece cover.

FURTHER INFORMATION

REMEMBER. This medicine is for YOU. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are similar.

This leaflet does not tell you everything about your medicine. If you have any questions or are not sure about anything, ask your doctor, nurse or pharmacist.

You will be able to find more information about prescribed medicine from books in public libraries.

The information in this leaflet only applies to Serevent Inhaler.

ALLEN & HANBURYS

817400/03

ACTION ASTHMA

PLEASE SEND ME AN ACTION ASTHMA INFORMATION PACK.
(PLEASE FILL IN THE LEAFLET CAREFULLY USING BLOCK CAPITALS)

Age group (tick appropriate box), and year of birth

☐ over 18 ☐ 11-18 Year

TITLE (OF PATIENT) MR/MRS/MS/MISS (delete as appropriate)

SURNAME INITIALS

ADDRESS

POSTCODE

Doctor's name and surgery address:

SURNAME INITIALS

ADDRESS

POSTCODE

N.B. We will send the Action Asthma Information pack even if you prefer not to fill in the doctor's name and address.

520E

- Do not store the inhaler above 30°C (86°F). Do not refrigerate or freeze. Protect from frost and direct sunlight.
- If the inhaler gets very cold, take the metal canister out of the plastic case and warm it IN YOUR HANDS for a few minutes before use. NEVER use anything else to warm it up.
- WARNING. The metal canister is pressurised. Do not puncture, break or burn it even when you think it is empty.
- Do not use after the date shown as 'EXP' on the carton and label.
- If you are told to stop taking this medicine, RETURN ANY FLIXOTIDE EVOHALERS TO YOUR PHARMACIST to be destroyed.

LEAFLET PREPARED MARCH 2003

HOW TO USE YOUR INHALER

1 To remove the mouthpiece cover, hold between the thumb and forefinger, squeeze gently and pull apart as shown. Check inside and outside to make sure that the mouthpiece is clean, and that there are no foreign objects.

TESTING YOUR INHALER
If your inhaler is new, or if it has not been used for a week or more, shake it well and release one puff into the air to make sure that it works.

2 Shake the inhaler before use.

3 Hold the inhaler upright as shown above with your thumb on the base, below the mouthpiece. Breathe out as far as is comfortable and then....

4 place the mouthpiece in your mouth between your teeth and close your lips around it but do not bite it.

5 Just after starting to breathe in through your mouth press down on the top of the inhaler to release a puff while still breathing in steadily and deeply.

6 Hold your breath, take the inhaler from your mouth and your finger from the top of the inhaler. Continue holding your breath for a few seconds or as long as is comfortable.

7 If you are to take another puff, keep the inhaler upright and wait about half a minute before repeating steps 2 to 6.

8 After use always replace the mouthpiece cover to keep out dust and fluff. REPLACE FIRMLY AND SNAP INTO POSITION.

IMPORTANT
Do not rush Stages 3, 4 and 5.
It is important that you start to breathe in as slowly as possible just before operating your inhaler. Practise in front of a mirror for the first few times. If you see 'mist' coming from the top of the inhaler or the sides of your mouth you should start again from Stage 2.

People with weak hands should hold the inhaler with both hands as shown opposite. Put the two forefingers on top of the inhaler and both thumbs on the base below the mouthpiece. (If this does not help, a special device called a Haleraid™ may make it easier. Your doctor, nurse or pharmacist will be able to advise you.)
If you have been given different instructions for using your inhaler, please follow them carefully. Tell your doctor, nurse or pharmacist if you have any difficulties.

CLEANING

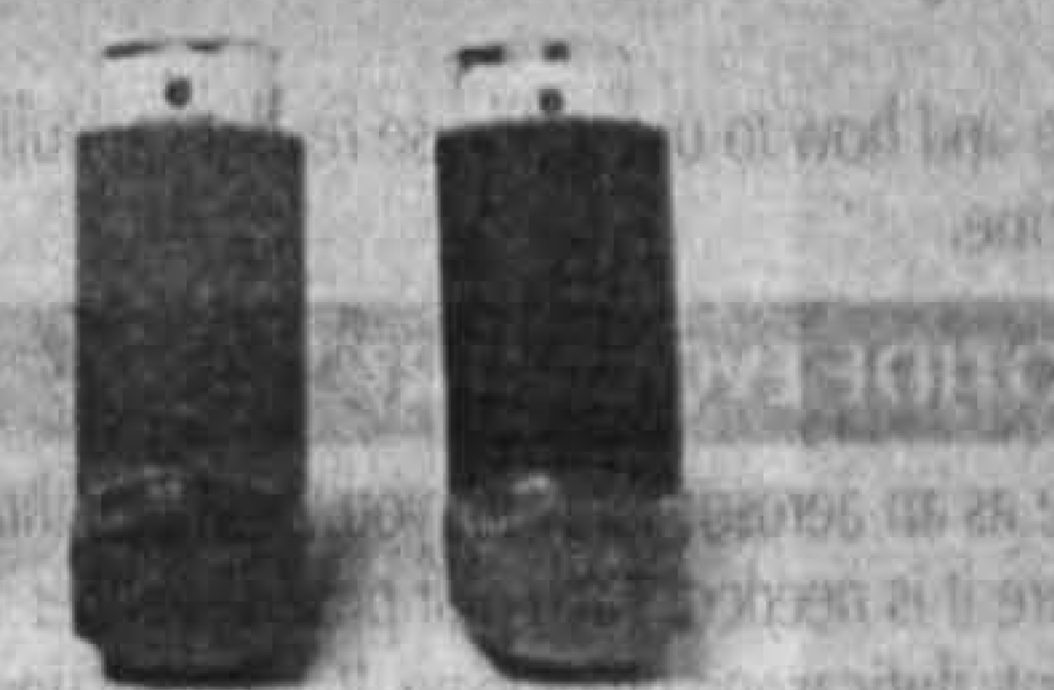
To prevent your inhaler blocking up, it is important to clean it at least once a week, following the instructions below. If your inhaler does block up, the same cleaning instructions should be followed.

To clean your inhaler:
Your inhaler should be cleaned at least once a week.
1. Pull the metal canister out of the plastic case of the inhaler and remove the mouthpiece cover.
2. Rinse the plastic case and the mouthpiece cover in warm water. If you notice a build up of medicine around the mouthpiece, do not attempt to unblock it with a sharp object, such as a pin. A mild detergent or a solution of the type used to clean babies feeding bottles may be added to the water (your pharmacist will advise you). Then rinse thoroughly with clean water before drying. Do not put the metal canister into water.
3. Leave the plastic case and the mouthpiece cover to dry in a warm place. Avoid excessive heat.
4. Replace the canister and mouthpiece cover.

FURTHER INFORMATION

REMEMBER: This medicine is for YOU. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are similar.
This leaflet does not tell you everything about your medicine. If you have any questions or are not sure about anything, ask your doctor or the pharmacist.
You will be able to find more information about prescribed medicines from books in public libraries.
The information in this leaflet only applies to Flixotide Evohaler.
Evohaler, Flixotide, Haleraid and Volumatic are trademarks of the Glaxo Wellcome Group of Companies.

ALLEN & HANBURYS



ALLEN & HANBURYS

Flixotide™ 125 mcg Evohaler™
Flixotide™ 250 mcg Evohaler™
fluticasone propionate

Please read the leaflet before using your Evohaler

NEW INFORMATION

For patients previously taking Flixotide Inhaler
This pack contains Flixotide Evohaler. You should use it exactly as instructed by your doctor.
The active ingredient in this **Flixotide Evohaler** is exactly the same as in your previous **Flixotide Inhaler**. The only differences that you might notice are the taste and the feel of the spray in your mouth, and the sound of the inhaler on using it. This does not affect the way your medicine works. You can use your **Flixotide Evohaler** in the same way as your previous **Flixotide Inhaler**, although you may find that it needs cleaning at least once a week. This instruction is the same as that provided with your previous Flixotide Inhaler. Please follow the cleaning instructions given at the end of this leaflet. If you have any questions about your treatment please contact your doctor, practice nurse or pharmacist or call Allen & Hanburys on 0800 371 891.

nt Information Leaflet for Flixotide 125 micrograms and 250 micrograms Evohaler
doctor has decided to prescribe Flixotide Evohaler as part of your treatment. This
cine is available in more than one strength. Your doctor will have decided which
gth you need.
leaflet tells you about your medicine and how to use it. Please read it carefully and
it until you have finished the medicine.

WHAT IS FLIXOTIDE EVOHALER?

tide Evohaler delivers your medicine as an aerosol spray for you to inhale, through
mouth, directly into your lungs where it is needed. Each puff provides either 125
0 micrograms of the active ingredient, fluticasone propionate. It also contains a
ellant, HFA 134a. Flixotide Evohaler contains the same medicine as Flixotide
er but may taste slightly different because the propellant gas is different.
canister provides 120 puffs.

WHO MAKES YOUR MEDICINE?

tide Evohaler is made by Glaxo Wellcome Operations, Greenford, Middlesex, UB6
The product licences are held by Allen & Hanburys, Stockley Park, Middlesex,
1BT.

HOW YOUR MEDICINE WORKS

asone propionate is one of a group of medicines called corticosteroids which are
referred to simply as 'steroids'. Corticosteroids are used to treat asthma because
ave an anti-inflammatory action. They reduce the swelling and irritation in the
of the small air passages in the lungs, and so ease breathing problems.
osteroids also help to prevent attacks of asthma. This is why they are called
nters'. Fluticasone propionate should be taken regularly every day.
sone propionate should not be confused with other steroids such as anabolic
s misused by some athletes and taken as tablets or injection.

USES

le Evohaler is used to prevent and treat asthma in people who need regular treatment.

KE SURE THAT THIS MEDICINE IS SUITABLE FOR YOU

OUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE

u are pregnant (or intending to become pregnant),
u are breast-feeding a baby,
u have ever had to stop taking this or another medicine for this illness because
vere allergic to it or it caused problems,
are having other regular treatment, such as certain medicines used to treat fungal
ions (e.g. ketoconazole) or a type of antiviral medicine known as a protease
tor (e.g. ritonavir). Check with your pharmacist or doctor if you are not sure,
are being, or have ever been, treated for tuberculosis (TB).

nes this medicine may not be suitable and your doctor may want to give you
ng different.
re that your doctor knows what other medicines you are taking (e.g. other inhalers,
ablets), including those you have bought from a pharmacy (chemist). Remember to
e medicines with you if you have to go into hospital.
ve just started to use a Flixotide Evohaler instead of, or as well as, taking
ablets, you should continue to carry a 'steroid warning card' (if you have one)
r doctor tells you that you don't need to any longer.

TAKING YOUR MEDICINE

ER that Flixotide Evohaler produces a fine mist which you must inhale into your
ake sure that you know how to use the inhaler properly. The instructions are

given later on in this leaflet. If you have problems ask your doctor, nurse or pharmacist. MAKE SURE YOU KNOW HOW AND WHEN TO USE YOUR INHALER, AND HOW MANY PUFFS TO TAKE. Your doctor should have told you and the instructions should be on the pharmacist's label. If they are not, or you are not sure, ask your doctor or pharmacist.

DOSE

For adults and children over 16 years of age: 100 to 1,000 micrograms TWICE a day.
For patients with mild asthma, the usual starting dose will be 100 micrograms TWICE a day.
Your doctor may give you a Flixotide Evohaler of a higher strength if he/she increases your dose.
For patients with moderate or severe asthma, the usual starting dose can vary from 250 to 500 micrograms TWICE a day:
TWO puffs of Flixotide Evohaler 125 micrograms TWICE a day to
TWO puffs of Flixotide Evohaler 250 micrograms (or FOUR puffs of Flixotide Evohaler 125 micrograms) TWICE a day.
If you suffer from severe asthma, your doctor may increase your dose to a maximum of 1,000 micrograms TWICE a day:
FOUR puffs of Flixotide Evohaler 250 micrograms TWICE a day.
From time to time, your doctor may change your dose. This is to find the lowest dose that gives you the best control of your asthma.
The starting dose will depend on your condition and will be decided by your doctor. Your doctor will prescribe the lowest dose of Flixotide Evohaler that will best control your symptoms. Flixotide Evohaler is available in lower strengths if needed.
Flixotide Evohaler 125 micrograms and Flixotide Evohaler 250 micrograms are not suitable for children under 16.

- People who are on higher doses (above 1,000 micrograms daily) should take their medicines via the Volumatic™ large-volume spacer device to help reduce side-effects in the mouth and throat. Your doctor, nurse or pharmacist will be able to advise you about this.
- Some people find it difficult to release a puff of medicine just after they start to breathe in. The Volumatic™ large-volume spacer device helps to overcome this problem. Your doctor, nurse or pharmacist will be able to advise you about this.
- IT IS VERY IMPORTANT that you keep to your doctor's instructions as to how many puffs to inhale and how often to use your Flixotide Evohaler. DO NOT USE more than you were told to.
- It takes a few days for this medicine to work and it is VERY IMPORTANT THAT YOU USE IT REGULARLY. DO NOT STOP treatment even if you feel better unless told to do so by your doctor.
- DO NOT USE THIS MEDICINE TO TREAT A SUDDEN ATTACK OF BREATHLESSNESS - it will not help you. You should use a quick-acting 'reliever' inhaler (e.g. salbutamol) for this purpose, which you should have available at all times. If you have more than one medicine be careful not to confuse them.

IF YOU TAKE TOO MUCH

- Tell your doctor as soon as possible if you accidentally take a larger dose than you were told to.

IF YOU MISS A DOSE

- If you miss a dose just take the next dose when it is due.

AFTER USING YOUR INHALER

- IF YOUR BREATHING OR WHEEZING GETS WORSE STRAIGHT AFTER USING YOUR INHALER, STOP USING IT IMMEDIATELY, AND TELL YOUR DOCTOR

STRAIGHTAWAY. YOU MAY NEED TO USE A QUICK-ACTING 'RELIEVER' INHALER TO TREAT YOUR SYMPTOMS.

- If you start to get worse (e.g. you feel wheezy or need more of your 'reliever' inhaler or 'reliever' medicine), or if you don't start to get better after 7 days, tell your doctor. He or she might want to increase your dose of Flixotide Evohaler, or change your medicine.
- If you are transferring from steroid tablets to Flixotide Evohaler you may find that, even if your chest is getting better, you feel a bit poorly. Sometimes treatment with Flixotide Evohaler can bring out certain allergies such as allergic rhinitis (including hayfever) or eczema, which may have been controlled before with your steroid tablets. Speak to your doctor about any symptoms such as these, but DO NOT STOP treatment unless you are told to.
- If you are being treated for a long time with high doses of inhaled steroid, you may require extra steroids in times of extreme stress or during admission to hospital after a serious accident or injury or before a surgical operation. Your doctor may decide to give you extra steroid medication during this period as tablets, or injection if you are in hospital.

SIDE-EFFECTS

Most people do not have any problems when taking this medicine.

- Some people occasionally develop thrush (a fungal infection) in their mouth and find that their tongue becomes sore, or that their voice becomes hoarse, or their throat becomes irritated, after inhaling this medicine. Brushing your teeth using plenty of water, or rinsing your mouth or gargling with water and spitting it out immediately after each dose may help. Tell your doctor but do not stop treatment unless you are told to. Your doctor may prescribe a spacer to help you with these side effects.
- A very few people may develop a skin rash or swelling e.g. of their hands, feet, face or throat.
- Very occasionally some people have noticed joint pains or indigestion. These may not have been due to this medicine.
- In rare instances, treatment with Flixotide Evohaler may affect the normal production of steroids in the body. This is more likely to happen if high doses (for example doses higher than 400 mcg daily in children) are being used over a long period of time. One of the rare effects is that children and adolescents may grow more slowly than others. Children and adolescents who are receiving treatment over a long period of time will have their height checked regularly by their doctor. Other effects are thinning of the bones and certain eye disorders (known as cataract and glaucoma). If you have just started using a spacer with your inhaler then your doctor may reduce your dose to decrease the risk of you getting these side effects.
  It is important that if you or your child is on high doses of inhaled steroid and become unwell with vague symptoms such as tummy ache, sickness, diarrhoea, headache or drowsiness you see a doctor immediately. This is more likely to happen during an infection such as a viral infection or stomach upset. It is important that your steroid is not stopped suddenly as this could make your asthma worse and could also cause problems with the body's hormones. If you or your child develops an illness like this, you should make sure that the doctor knows that you/your child is on inhaled steroids and the daily dose. Check with your doctor if you are uncertain.

Your doctor will help to prevent these possible side effects by prescribing the lowest dose of Flixotide at which your asthma is well controlled.
If you feel unwell or notice anything unusual or which you don't understand, tell your doctor as soon as possible.

LOOKING AFTER YOUR MEDICINE

- Keep your inhaler in a safe place WHERE CHILDREN CANNOT REACH IT.
- Clean your inhaler on a weekly basis as described under **CLEANING.**
- If your inhaler becomes blocked, it should be washed as described under **CLEANING.**

817400/03

ACTION ASTHMA

WELCOME TO THE ACTION ASTHMA PATIENT SERVICE. This Service offers you personalised information and support. It aims to provide the information you need to lead an active and enjoyable life, whilst managing your asthma with confidence. It is intended to complement the advice and support which you already receive from your doctor, nurse or pharmacist.
The Service has been developed with the help of a group of doctors with a special interest in asthma. It is available to adults and children with asthma.

The Action Asthma Patient Service offers:-

* A specifically designed information pack.
* A special questionnaire 'You and your asthma' for you to fill in and return. This helps us to provide the information you need on your asthma.
* Further information and offers.
* Telephone advice lines as follows:
  1. More information about asthma 020 8990 3011
  2. Practical advice for the asthmatic patient 020 8990 2430

Please note: you will have to pay for the call, but each message lasts less than 6 minutes.

IF YOU WOULD LIKE TO RECEIVE THE ACTION ASTHMA PATIENT SERVICE, PLEASE FOLLOW THESE INSTRUCTIONS.

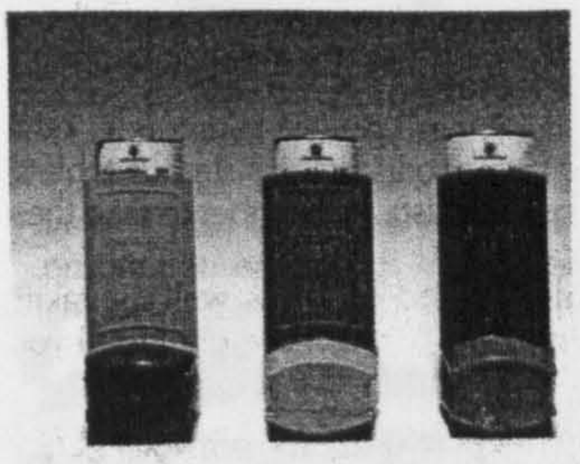
1. Please fill in the other side of this leaflet clearly.
2. Cut out this section of the leaflet and send it to the following address:

Action Asthma Patient Service
Department G
FREEPOST DR83
ASHFORD
KENT TN24 0YX
(There is no need to use a stamp)

3. Please allow 28 days for delivery.

This Service is available to anyone who lives in the UK, or is serving in the British Armed Forces.

PLEASE RETURN THIS SECTION OF THE LEAFLET ONLY



ALLEN & HANBURYS

Seretide™ Evohaler™

Patient Information Leaflet for Seretide 50 Evohaler, Seretide 125 Evohaler and Seretide 250 Evohaler. This pack contains both a 'preventer' and a 'protector' in a single inhaler.

Your doctor has prescribed you a Seretide Evohaler as part of your treatment. Seretide Evohaler is available in several strengths. Your doctor will have decided which strength you need. Seretide 50 Evohaler is recommended for use in children older than 4 years of age. All three strengths are recommended for use in adults and adolescents 12 years of age and over.

This leaflet tells you about your Seretide Evohaler and how to use and clean it. Please read the leaflet carefully before using your inhaler and keep it until you have finished the medicine. You may find that your inhaler needs cleaning at least once a week. Please follow the cleaning instructions given at the end of this leaflet.

WHAT IS SERETIDE EVOHALER?

Seretide Evohaler delivers your medicine as a pressurised suspension for inhalation for you to inhale, which delivers your medicine directly into your lungs where it is needed. Each puff provides 25 micrograms of the active ingredient salmeterol (as the xinafoate) together with either 50, 125 or 250 micrograms of the active ingredient fluticasone propionate. It also contains a CFC-free propellant, Norflurane (HFA 134a). Each container provides 120 puffs.

WHO MAKES YOUR MEDICINE?

Seretide Evohaler is manufactured by Glaxo Wellcome Production, Zone Industrielle N°2, 23 Rue Lavoisier, 27000 Evreux, France. The product licence is held by Allen & Hanburys, Stockley Park, Middlesex, UB11 1BT.

HOW YOUR MEDICINE WORKS

Your medicine contains two active ingredients:

Salmeterol xinafoate is one of a group of medicines called long-acting bronchodilators. It relaxes the muscles in the walls of the small air passages in the lungs. This helps to open up the airways and makes it easier for air to get in and out of the lungs. The effects of salmeterol xinafoate usually last for at least twelve hours. When it is taken regularly, it helps the small air passages to STAY OPEN. This is why salmeterol xinafoate is called a 'protector'.

Fluticasone propionate is one of a group of medicines called corticosteroids which are often referred to simply as 'steroids'. Corticosteroids are used to treat asthma because they have an anti-inflammatory action. They reduce the swelling and irritation in the walls of the small air passages in the lungs, and so ease breathing problems. Corticosteroids also help to prevent attacks of asthma. This is why they are called 'preventers'. Fluticasone propionate should be taken regularly every day. Fluticasone propionate should not be confused with other steroids such as anabolic steroids misused by some athletes and taken as tablets or injection.

Seretide Evohaler contains both a 'preventer' and a 'protector' in a single inhaler. If your doctor has prescribed you a Seretide Evohaler, you should not use an additional corticosteroid (preventer) inhaler unless your doctor tells you to do so.

USES

Seretide Evohaler is used for the regular treatment of asthma, in adults and children aged 4 and over. Seretide 50 Evohaler should not be used in adults and children with severe asthma.

MAKE SURE THAT THIS MEDICINE IS SUITABLE FOR YOU

TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE

* if you have ever had to stop taking this or another medicine for this illness because you were allergic to it or it caused problems,
* if you are pregnant (or intending to become pregnant),
* if you are breast-feeding a baby,
* if you are being, or have ever been, treated for tuberculosis (TB),
* if you are having treatment for an overactive thyroid condition,
* if you have diabetes mellitus,
* if you have heart disease,
* if you are having treatment for high blood pressure,
* if you have an irregular heart beat/rhythm, including a very fast pulse,
* if you have a low level of potassium in your blood.

Sometimes this medicine may not be suitable and your doctor may want to give you something different.

In some cases, Seretide may not be suitable to use with other medicines so be sure to tell your doctor:

* if you have recently been treated with steroid injections, or if you have been taking oral steroids for a long time,
* if you are taking any medicines called 'beta blockers' (e.g. atenolol, propranolol, sotalol, etc.),

4 place the mouthpiece in your mouth between your teeth and close your lips around it but do not bite it.

5 Just after starting to breathe in through your mouth, press down on the top of the inhaler to release a puff while still breathing in steadily and deeply.

6 Hold your breath, take the inhaler from your mouth and your finger from the top of the inhaler. Continue holding your breath for a few seconds, or as long as is comfortable.

7 When you take another puff, keep the inhaler upright and wait about half a minute before repeating steps 2 to 6.

8 After use, always replace the mouthpiece cover to keep out dust and fluff. REPLACE MOUTHPIECE COVER FIRMLY AND SNAP INTO POSITION.

IMPORTANT

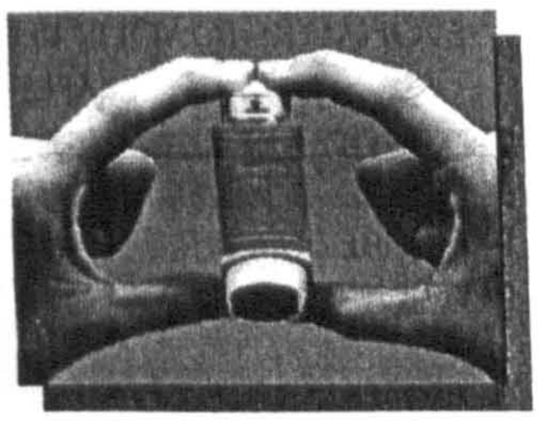
Do not rush stages 3, 4 and 5.

It is important that you start to breathe in as slowly as possible just before operating your inhaler. Practise in front of a mirror for the first few times. If you see 'mist' coming from the top of the inhaler or the sides of your mouth, you should start again from Stage 2.

Some people find it difficult to release a puff of medicine just after they start to breathe in. The Volumatic™ large-volume spacer device helps to overcome this problem. Your doctor, nurse or pharmacist will be able to advise you about this.

People with weak hands may find it easier to hold the inhaler with both hands as shown. Put the two forefingers on top of the inhaler and both thumbs on the bottom below the mouthpiece. If this does not help, a special device called a Haleraid™ may make it easier. Your doctor, nurse or pharmacist will be able to advise you.

If you have been given different instructions for using your inhaler, please follow them carefully. Tell your doctor, nurse or pharmacist if you have any difficulties.



CLEANING

To prevent your inhaler blocking up, it is important to clean it at least once a week, following the instructions below. If your inhaler does block up, the same cleaning instructions should be followed. If you notice a build up of medicine around the mouthpiece, do not attempt to unblock it with a sharp object, such as a pin.

To clean your inhaler:

1. Remove the mouthpiece cover.
2. Do not remove the container from the plastic casing.
3. Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth, tissue or cottonbud. Do not put the metal container into water.
4. Replace the mouthpiece cover.

FURTHER INFORMATION

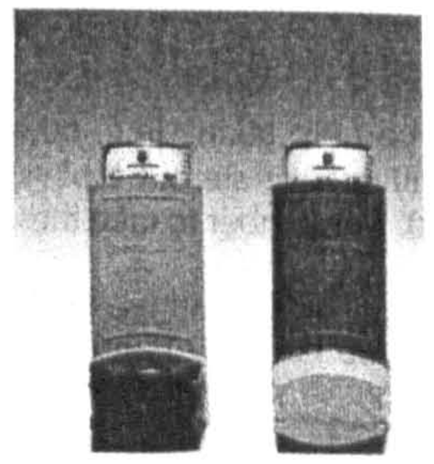
REMEMBER. This medicine is for YOU. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are similar. This leaflet does not tell you everything about your medicine. If you have any questions or are not sure about anything, ask your doctor, nurse or pharmacist.

You will be able to find more information about prescribed medicines from books in public libraries.

The information in this leaflet only applies to Seretide Evohaler.

Evohaler, Haleraid, Seretide and Volumatic are trademarks of the GlaxoSmithKline group of companies.

ALLEN & HANBURYS



Patient Information Leaf
Seretide 250 Evohaler. Th
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WHA

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HOW

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Sometimes this medicine ma
you something different.
In some cases, Seretide may n
to tell your doctor:

* if you have recently been
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* if you are taking any medici
sotalol, etc.),
* if you are taking a type of

* if you are taking any medicines to control an irregular heart beat/rhythm, including a very fast pulse.

Check with your pharmacist or doctor if you are not sure.

Make sure that your doctor knows what other medicines you are taking (e.g. other inhalers, treatment to reduce fluid, any kind of bronchodilators or steroid tablets), including those you have bought from a pharmacy (chemist). Remember to take these medicines with you if you have to go into hospital.

If you have just started to use a Seretide Evohaler instead of, or as well as, taking steroid tablets, you should carry a 'steroid warning card' (if you have one) until your doctor tells you that you don't need to any longer.

TAKING YOUR MEDICINE

* REMEMBER that Seretide Evohaler produces a fine mist which you must inhale through your mouth into your lungs. Make sure that you know how to use the inhaler properly. The instructions are given later on in this leaflet. If you have problems, ask your doctor, nurse or pharmacist.
* MAKE SURE YOU KNOW HOW AND WHEN TO USE YOUR INHALER, AND HOW MANY PUFFS TO TAKE. Your doctor should have told you and the instructions should be on the pharmacist's label. If they are not, or you are not sure, ask your doctor or pharmacist.

DOSE

For adults and adolescents 12 years of age and over:
Seretide 50 Evohaler: Two puffs twice a day
Seretide 125 Evohaler: Two puffs twice a day
Seretide 250 Evohaler: Two puffs twice a day

For children 4 to 12 years of age:
Seretide 50 Evohaler: Two puffs twice a day

This medicine is NOT recommended for children below 4 years of age.

The strength will depend on your condition and will be decided by your doctor. Your doctor will prescribe the lowest strength of Seretide Evohaler that will best control your symptoms. If your symptoms are very well controlled using Seretide Evohaler twice a day, your doctor may decide to reduce your dose to once a day. This may be either once a night, if you have night-time asthma symptoms, or once in the morning if you usually have daytime symptoms.

* IT IS VERY IMPORTANT that you keep to your doctors' instructions as to how many puffs to inhale and how often to use your Seretide Evohaler. DO NOT USE more often than you were told to.
* It is VERY IMPORTANT THAT YOU USE YOUR SERETIDE EVOHALER EVERY DAY. DO NOT STOP treatment even if you feel better unless told to do so by your doctor.
* DO NOT USE THIS MEDICINE TO TREAT A SUDDEN ATTACK OF BREATHLESSNESS - it will not help you. You should use a quick-acting 'reliever' inhaler (e.g. salbutamol) for this purpose, which you should have available at all times. If you have more than one medicine, be careful not to confuse them.
* A spacer device may be used, particularly with young children, if you or your child have difficulty co-ordinating breathing in through your mouth and pressing down on the top of the inhaler to release a puff at the same time.

IF YOU TAKE TOO MUCH

It is important to keep to the dose on the pharmacist's label. If you accidentally take a LARGER DOSE THAN RECOMMENDED, you may notice that your heart is beating faster than usual and that you feel shaky. You may also have a headache. Contact your doctor as soon as possible for advice.

IF YOU MISS A DOSE

If you forget a dose, do not worry. Inhale a dose when you remember, then go on as before.

AFTER TAKING YOUR MEDICINE

* IF YOUR BREATHING OR WHEEZING GETS WORSE STRAIGHT AFTER USING YOUR INHALER, STOP USING IT IMMEDIATELY, AND TELL YOUR DOCTOR STRAIGHTAWAY.
* If your asthma gets worse or is not well-controlled (e.g. you feel wheezy or need more of your 'reliever' inhaler), go and see your doctor. If your 'reliever' inhaler does not improve your asthma, you must see your doctor as soon as possible. Your chest condition may be getting worse and the doctor may need to increase your amount of inhaled steroid.
* If you are being treated for a long time with high doses of any inhaled steroid, you may require extra steroids in times of extreme stress or during admission to hospital after a serious accident or injury or before a surgical operation. Your doctor may decide to give you extra steroid medication during this period as tablets, or injection if you are in hospital.

SIDE EFFECTS

Most people do not have any problems when taking this medicine.

* Some people may be allergic to this medicine. If you develop a rash or swelling (usually of the face, mouth or throat), stop using your Seretide Evohaler and tell your doctor straightaway.
* Some people may occasionally feel a bit shaky or have a headache, but these effects usually wear off as treatment continues.
* Some people who are unusually sensitive may notice that their heart is beating faster than usual. This awareness of their heart beating is called palpitations, is normally harmless, and usually passes off as treatment continues. Some might

* Some people occasionally develop 'thrush' in their mouth and find that their tongue becomes sore, their voice becomes hoarse, or their throat becomes irritated, after inhaling this medicine. Rinsing the mouth with water and spitting it out immediately after each dose may help. Your doctor may prescribe a spacer to help you with these side effects.
* In very rare instances, treatment with Seretide Evohaler may affect the normal production of steroids in the body. This is more likely to happen if high doses are being used over a long period of time (for example if using more than 2 inhalations Seretide 50 Evohaler twice daily in children). One of the rare effects is that children and adolescents may grow more slowly than others. Children and adolescents who are receiving treatment over a long period of time should have their height checked regularly by their doctor. Other effects are thinning of the bones and certain eye disorders (known as cataract and glaucoma). These effects are much less likely to occur than with steroid tablets. If you have just started using a spacer with your inhaler then your doctor may reduce your dose to decrease the risk of you getting these side effects.

It is important that if you or your child is on high doses of inhaled steroid and becomes unwell with vague symptoms such as tummy ache, sickness, diarrhoea, headache or drowsiness you see a doctor immediately. This is more likely to happen during an infection such as a viral infection or a stomach upset. It is important that your steroid is not stopped suddenly as this could make your asthma worse and could also cause problems with the body's hormones. If you or your child develops an illness like this, you should make sure that the doctor knows you/your child is on inhaled steroids and the daily dose. Check with your doctor if you are uncertain.

Your doctor will help prevent these possible side effects by prescribing the lowest dose of Seretide at which your asthma is well-controlled.

If you feel unwell or notice anything unusual which you don't understand, tell your doctor as soon as possible.

LOOKING AFTER YOUR MEDICINE

* Keep your Seretide Evohaler in a safe place WHERE CHILDREN CANNOT REACH IT.
* Clean your inhaler on a weekly basis as described under **CLEANING.**
* If your inhaler becomes blocked, it should be washed as described under **CLEANING.**
* Do not store the inhaler above 25°C.
* If the inhaler gets very cold, take the metal container out of the plastic case and warm it IN YOUR HANDS for a few minutes before use. NEVER use anything else to warm it up.
* WARNING. The metal container is pressurised. Do not puncture, break or burn it even when apparently empty.
* Do not use after the date shown as 'EXP' on the carton and label.
* If you are told to stop taking this medicine, RETURN ANY SERETIDE EVOHALERS TO YOUR PHARMACIST to be destroyed.

LEAFLET PREPARED FEBRUARY 2004

HOW TO USE YOUR INHALER

REMEMBER: Your doctor, nurse or pharmacist should instruct you in the proper use of your Seretide Evohaler.

1 To remove the snap-on mouthpiece cover, hold between the thumb and forefinger, squeeze gently and pull apart as shown. Check inside and outside to make sure that the mouthpiece is clean, and that there are no foreign objects.

TESTING YOUR INHALER

If your inhaler is new or if it has not been used for a week or more, shake it well and release two puffs into the air to make sure that it works.

2 Shake the inhaler before use.

3 Hold the inhaler upright as shown above with your thumb on the base, below the mouthpiece. Breathe out as far as is comfortable and then.....

APPENDIX 5

Peer Review Publications in International Journals

ASTHMA

Impact of changes in the IOC-MC asthma criteria: a British perspective

J W Dickinson, G P Whyte, A K McConnell, M G Harries

Thorax 2005;60:629–632. doi: 10.1136/thx.2004.037499

See end of article for authors' affiliations

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Received 11 November 2004
Accepted 29 March 2005

Background: Since 2001 the International Olympic Committee-Medical Commission (IOC-MC) has required athletes using inhaled β_2 agonists to provide clinical evidence of their asthmatic condition. The aim of this study was to compare the reported prevalence of asthma at the 2000 and 2004 Olympic Games in the Great British Olympic team (Team GB).

Methods: Following local ethics committee approval, 271 athletes (165 men) from the 2004 Team GB volunteered and provided written informed consent. An athlete was confirmed asthmatic if he or she had a positive bronchoprovocation or bronchodilator test as defined by the IOC-MC. Pre-Olympic medical forms from the 2000 Team GB were also examined to establish the prevalence of asthma among the members of Team GB at the 2000 Olympic Games.

Results: The prevalence of asthma in the two teams at the 2000 and 2004 Olympic Games was similar (21.2% and 20.7%, respectively). In the 2004 Olympic Games 13 of 62 athletes (21.0%) with a previous diagnosis of asthma tested negative. A further seven with no previous diagnosis of asthma tested positive.

Conclusions: The prevalence of asthma within Team GB remained unchanged between 2000 and 2004. The IOC-MC requirement that asthmatic athletes must submit documented evidence of asthma has highlighted that 13 (21.0%) previously diagnosed as asthmatic failed to demonstrate evidence of asthma while seven athletes with no previous history or diagnosis of asthma tested positive. Screening for asthma within elite athletic populations using bronchoprovocation challenges appears warranted to assist athletes in preparing more effectively for major sporting events.

Exercise induced asthma (EIA) causes expiratory limitation following exercise. It can be triggered by an increase in the volume of "unconditioned" air inspired through the mouth. During increased levels of activity "unconditioned" air cools and dries the upper and lower airways inducing inflammation and smooth muscle contraction leading to bronchial narrowing[1] that is readily reversible with inhaled short acting β_2 agonists. The prevalence of EIA in athletic populations has been shown to vary between 9% and 55%,[2 3] depending on the type of sport, diagnostic test used, and environment. Participants in winter sports generally have a higher prevalence of EIA than those engaged in summer sports.[4–7]

A number of studies have shown that therapeutic doses of inhaled short acting β_2 agonists have no performance enhancing effects,[8–11] yet the International Olympic Committee-Medical Commission (IOC-MC) has stated that a simple notification from the team medical officer stating the athlete has EIA is no longer acceptable.[12] A more rigorous testing regime including maximal voluntary flow-volume loops is now required.[13]

One of the main reasons the IOC-MC has given for the enhanced level of evidence is an apparent increase in the prevalence of asthmatic athletes since the 1984 Olympic Games.[13] At the 1984 Los Angles Olympics 11% of the US Olympic team were using inhalers.[14] The prevalence of asthma reported within the US team at the 1996 Olympics in Atlanta was 14%,[4] and by 1998 at the Winter Olympics in Nagano this figure had reached 17%.[5] While there seems to be a progressive rise in EIA within the US Olympic teams, there are limited reports on the prevalence of asthma in the Olympic teams of other nations. What remains unclear is whether the observed increase in the prevalence of asthma in the US teams is an indication of a global trend at the elite athletic level. Further, there are few data available on sport specific prevalence.[15]

Many studies have reported the prevalence of asthma by the sole use of questionnaires and symptoms.[4 5 14 16–19] This approach, however, is regarded as a poor method of assessment. For example, Rundell *et al*[20] examined the accuracy of symptom based diagnosis compared with an exercise challenge to diagnose EIA in elite winter athletes by comparing results from an asthma symptoms questionnaire with those from exercise challenge. Of the 26% of participants who tested positive for EIA in response to the exercise challenge, only 40% of these reported more than one symptom of EIA in the questionnaire. Post-exercise cough was the most common symptom reported by both EIA positive and EIA negative athletes. The high number of false positives and false negatives from questionnaire diagnosis highlights the need for bronchoprovocation tests and supports the IOC-MC requirement for athletes to produce quantitative evidence of their asthma.

The relative paucity of sport specific data examining the prevalence of asthma/EIA, together with the IOC-MC changes in criteria for asthma diagnosis, provide the rationale for this study. The purpose of this study was to compare the prevalence of EIA within the Great British Olympic Team (Team GB) at the 2000 and 2004 Summer Olympic Games, to quantify sport specific differences in the prevalence of EIA, and to examine the implications of changes made in the IOC-MC guidelines.

Abbreviations: EIA, exercise induced asthma; EVH, eucapnic voluntary hyperpnoea; FEV_1, forced expiratory volume in 1 second

Table 1 Prevalence of asthma in the British squads at the 2000 and 2004 Olympic Games

	2000		2004	
	N	No (%) asthmatic	N	No (%) asthmatic
Athletics	28	7 (25)	58	9 (16)
Badminton	13	2 (15)	11	1 (9)
Canoe/kayak	12	1 (8)	9	1 (11)
Cycling	27	12 (44)	23	9 (39)
Diving	7	3 (43)	7	1 (14)
Gymnastics	14	0	9	0
Hockey	31	3 (10)	16	5 (31)
Judo	10	2 (20)	8	1 (13)
Rowing	41	8 (20)	36	7 (19)
Sailing	17	0	18	0
Shooting	6	0	6	1 (17)
Swimming	41	17 (41)	36	16 (44)
Triathlon	8	0	6	0
Other	19	3 (16)	28	5 (18)
Overall				
Men	152	29 (19.1)	165	34 (20.6)
Women	122	29 (23.8)	106	22 (20.8)
Total	274	58 (21.2)	271	56 (20.7)

METHODS

2004 Team GB

Following local ethical committee approval, British athletes (165 men, 106 women) selected to compete in the 2004 Team GB were recruited. All athletes were volunteers and provided written informed consent. Athletes were only tested for asthma if they had a previous diagnosis of EIA or reported symptoms of EIA or were referred for testing by a team medical officer.

IOC-MC criteria

Diagnosis of asthma for the 2004 Team GB members was made according to the IOC-MC requirements, which included a positive bronchodilator or bronchoprovocation test. The IOC-MC criteria for a positive diagnosis in a bronchodilator challenge were met if the forced expiratory volume in 1 second (FEV_1) increased by 15% or more following a therapeutic inhaled dose (200 μg) of a short acting β_2 agonist (salbutamol). The IOC-MC criteria for a positive diagnosis in a bronchoprovocation challenge were met if the post-challenge FEV_1 fell 10% or more from the pre-challenge FEV_1 measurement. Both bronchodilator and bronchoprovocation responses were assessed using maximal effort flow-volume spirometry, measured with an electronic spirometer that met American Thoracic Society guidelines (MicroLab ML3500, Micro Medical, Rochester, UK). The best of three criteria were applied for selection of recordings.

All asthma drug treatments including inhaled corticosteroids and long acting β_2 agonists were withdrawn for a minimum of 72 hours before each bronchial challenge. Athletes were advised to use short acting β_2 agonists if they required any asthma relief during this period.

Bronchodilator challenge

The bronchodilator challenge involved measuring maximal voluntary flow-volume loops before and 10 minutes after a therapeutic dose (200 μg) of an inhaled β_2 agonist (salbutamol).

Bronchoprovocation challenges

The bronchoprovocation challenges consisted of either an exercise challenge or eucapnic voluntary hyperpnoea (EVH) challenge.[21]

Exercise

An exercise challenge involved measuring maximal flow-volume loops before exercise and at 3, 5, 10 and 15 minutes after stopping exercise. The exercise challenges were conducted for a minimum of 4 minutes and were designed to be as sport specific as possible, so could involve running, cycling, rowing or swimming. The target heart rate (HR) during the exercise challenge was 80–90% of HRmax (220 − age).

Eucapnic voluntary hyperventilation (EVH)

The EVH challenges involved measuring maximal voluntary flow-volume loops before EVH (best of three) and at 3, 5, 10, and 15 minutes after stopping hyperventilation (single effort). The EVH challenge required the athlete to hyperventilate for 6 minutes at a rate of 30 times their baseline FEV_1. To prevent hypocapnia during hyperventilation, subjects inspired a gas mix containing 5% CO_2, 21% O_2, and 74% N_2.[21]

Prevalence of asthma in 2000 Team GB

Competitors' medical forms from the 2000 Team GB (120 women, 152 men) were used to obtain the reported prevalence of asthma before the IOC required quantitative evidence of asthma. Data obtained from these forms included the athletes' asthmatic status and event.

Analysis of data

The prevalence of asthma within each sport for 2000 Team GB and 2004 Team GB is reported descriptively by sport, sex, and overall prevalence.

RESULTS

Seventy seven athletes who were members of 2004 Team GB were tested for asthma using a test recognised by the IOC. All athletes required to provide evidence of asthma were tested. Sixty two of these athletes had been previously diagnosed with asthma and were prescribed asthma medication; 13 of these 62 (21%) failed to produce a positive test for asthma under IOC criteria. Of the 13 athletes, all reported symptoms of EIA with post exercise cough (n = 10), wheezing (n = 10), and chest tightness (n = 10). In addition to the 62 athletes receiving medication, a further 15 athletes referred by a team medical officer were tested. Seven of these 15 athletes (47%) had no previous history or diagnosis of asthma tested positive for asthma under IOC guidelines. Four of these seven athletes

reported symptoms of EIA with post exercise cough (n = 3), wheezing (n = 3), and chest tightness (n = 3) being the most common. The athletes who met the criteria to use asthma medication at the 2004 Olympic Games (n = 56) won a total of 17 medals (seven Gold, seven Silver, three Bronze). The athletes who failed to meet the IOC-MC criteria and were subsequently removed from asthma medication (n = 13) at the 2004 Olympic Games won a total of two medals (both Gold).

Of the 56 IOC-MC positive athletes, only two provided evidence of asthma through bronchodilator challenge; all the others required a bronchoprovocation challenge. The fall in FEV_1 elicited by the positive exercise challenges ranged from 10.5% to 23.3%. The fall in FEV_1 elicited by positive EVH challenges ranged from 10.0% to 61.3%. All athletes who had a positive bronchoprovocation challenge demonstrated reversibility.

The prevalence of asthma in the British squad at both the 2000 and 2004 Olympic Games is displayed in table 1 by sex, sport, and overall prevalence.

Swimming had the third highest prevalence of asthma in 2000 (41%) and the highest in 2004 (44%). Other sports in which the prevalence of asthma also remained similar between 2000 and 2004 included canoeing (8% *v* 11%), rowing (20% *v* 19%), and cycling (44% *vv* 39%). Sports in which there was a fall in the prevalence of asthma from 2000 to 2004 included athletics (25% *v* 16%), badminton (15% *v* 9%), diving (43% *v* 14%), and judo (20% *v* 13%). Sports that have seen an increase in the prevalence of asthma from 2000 to 2004 include archery (33% *v* 50%), men's hockey (13% *v* 31%), shooting (0% *v* 17%) and tae kwon do (0% *v* 25%). Sports that had no asthmatics in either 2000 or 2004 included boxing, gymnastics, modern pentathlon, sailing, tennis, weightlifting, and wrestling.

DISCUSSION

The main finding of this study was that the prevalence of EIA in Team GB athletes was unchanged between the 2000 and 2004 Olympic Games whereas, within the US Olympic team, it appears to be rising.[4 5 14] Unfortunately, it is impossible to determine precisely how the diagnoses of asthma in the US Olympic team were made, as they were conducted at a time when a range of different (unspecified) methods were employed. In the case of our own data, 21% of athletes previously diagnosed with asthma and using inhalers did not meet the IOC-MC criteria. This indicates that a large number of British Olympic athletes were receiving medication for which there was no clinical indication. The percentage of athletes in the 2004 Team GB squad who did not meet IOC-MC criteria is similar to the percentage of athletes whose application was declined by the IOC-MC at the 2002 Winter Olympics;[13] 29 of 159 (18%) of those who submitted an application to use β_2 agonists at the 2002 Winter Olympics were refused by the IOC-MC. We support the IOC-MC contention that a large number of athletes may be misdiagnosed and inappropriately medicated. The new IOC-MC asthma/EIA guidelines may therefore improve athlete care.

Despite identifying inappropriately medicated athletes and their subsequent withdrawal from medication, there was no overall change in the prevalence of asthma within Team GB between 2000 and 2004. This outcome is probably due to the identification of the small number (n = 7) of athletes with no previous history who had a positive response to bronchoprovocation. If diagnosis in the 2004 team had been based on symptoms alone, then the prevalence rate would have been 27% ([62+12]/271), which is higher than the actual prevalence rate and higher than the rate reported in 2000 (21%). This finding is consistent with previous studies that have shown a continued rise in the prevalence of asthma at Olympic Games.[4 5 13 14] Our data require substantiation by data from future Olympics using the new IOC-MC criteria.

The results from the present study show that there is variation between sports in the prevalence of asthma in Team GB Olympic teams, with swimming having one of the highest at both the 2000 and 2004 Olympics Games (>40%). It has been suggested that the high prevalence of asthma in swimmers may be due to the environment in which they train and compete, with a high concentration of chlorine which may act as a potent trigger for EIA.[22 23] Other sports such as figure skating and cross country skiing have also been reported to have a similarly high prevalence of asthma (35%, and 50%, respectively), which has been associated with training and competing in cold and dry or polluted environments.[6 24 25] This suggests that athletes who compete in certain sports may be more susceptible to the development of EIA than others. What is of great concern is that our data indicate that the overall prevalence of asthma is higher in elite athletes than it is in the general UK adult population (7.8%).[26] The factors underlying this observation require urgent attention since they have implications—not only for elite athletes—but also for the many recreational athletes in the UK and elsewhere.

The small number of athletes within some of the squads (archery, boxing, fencing, modern pentathlon, shooting, tae kwon doe, triathlon) makes it difficult to obtain an accurate impression of the prevalence of EIA/asthma by sport. Indeed, the prevalence data for triathlon appears to be inconsistent with our other findings. At the 2000 and 2004 Olympic Games the Team GB triathlon squad did not have one athlete diagnosed with asthma, yet swimming and cycling were among the sports with the highest prevalence of asthma at both the 2000 and 2004 Olympic Games. It is possible that the absence of triathletes with asthma in Team GB may be due to the small size of the squad and may not be a true representation of triathlon as a whole. Future investigations could overcome this by polling prevalence data from the Olympic teams of several countries. Multicentre data collection is indicated to support collection of prevalence data.

In a unique study by Alaranta *et al*[19] sports were classified into four main groups and the prevalence of EIA was reported on the basis of whether the sport was endurance, team, speed/power, or motor skill. The prevalence of EIA was highest in endurance sports (22.2%) and team sports (14.5%) compared with 8.8% for speed and power sports and 8.2% for motor skill sports. Unfortunately, the study relied solely on physician diagnosis and it lacked individual sport prevalence data. Our data used recognised EIA tests to gain the prevalence data at the 2004 Olympics and also examined the individual sports. It is difficult to make a direct comparison with the data from the study by Alaranta *et al*[19] as sports such as swimming and athletics have many different events ranging from sprinting to endurance events. Subdividing events into groups based on their aerobic requirement seems to suggest that events with a longer exposure to inhalation of "unconditioned" air (such as endurance events) could have a higher prevalence of EIA than events that involve shorter exposure to "unconditioned" air (such as sprint events), supporting the implication of the study by Alaranta *et al*.[19] Furthermore, sports/events that take place in environments that have a high potency for triggering EIA (such as dry/polluted air) may have the highest prevalence of asthma regardless of the duration of the activity (for example, winter sports/swimming). This interpretation suggests that the development of EIA may be exacerbated, or even caused, by a process of airway remodelling in response to training and competing in an environment that triggers EIA. This remodelling process may

occur at different speeds, depending on the individual, type of event, and environment.

The introduction of more rigorous testing procedures for the diagnosis of EIA/asthma resulted in 21% of athletes who were thought to be EIA positive being confirmed as EIA negative. This rate of misdiagnosis is not as high as that reported by Rundell *et al*[20] in their comparison of questionnaire diagnosis and diagnosis via exercise challenges (60%). One of the reasons for this could be the variety of different methods used to diagnose asthma in Team GB athletes in the past. Thus, not all of the athletes who took part in our study would have received a previous diagnosis based on symptoms alone. At present no systematic programme exists for the diagnosis of EIA/asthma in Team GB athletes. Such a programme could reduce the chance of false positive diagnoses and reduce the needless use of medication which may have potentially damaging side effects, such as downregulation of airway β_2 receptors.[27] Perhaps more importantly, this study identified seven athletes with no previous history or diagnosis of asthma, three of whom reported no symptoms of EIA on questioning. Some of them presented with falls in FEV_1 of more than 40% following EVH challenge. The implications of untreated EIA/asthma for the performance, health, and wellbeing of these athletes can only be speculated upon and argues strongly for the routine screening of all athletes.

In conclusion, the prevalence of asthma in 2004 Team GB athletes remained similar to that in 2000 Team GB athletes, despite changes in IOC-MC requirements. The improved diagnostic techniques, however, identified a large number of false positive diagnoses and also identified a number of previously unknown asthmatics. These athletes were either removed from unnecessary treatment or placed on appropriate medication, and therefore received an improved level of care. Screening for EIA within elite athletic populations using bronchoprovocation challenges such as EVH and exercise appears warranted, not only to assist athletes in preparing for major sporting events but also to ensure the best possible level of care.

ACKNOWLEDGEMENTS

The authors are grateful to the European Olympic Committee, UK Sport, British Olympic Medical Trust and Micro Medical Ltd (www.micromedical.co.uk).

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Competing interests: none declared

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ORIGINAL ARTICLE

Screening elite winter athletes for exercise induced asthma: a comparison of three challenge methods

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Br J Sports Med 2006;40:179–183. doi: 10.1136/bjsm.2005.022764

Background: The reported prevalence of exercise induced asthma (EIA) in elite winter athletes ranges from 9% to 50%. Many elite winter athletes do not report symptoms of EIA. At present there is no gold standard test for EIA.

Objective: To establish the efficacy of screening for EIA and examine the role of the eucapnic voluntary hyperventilation (EVH) challenge and laboratory based and sport specific exercise challenges in the evaluation of elite winter athletes.

Methods: 14 athletes (mean (SD) age 22.6 (5.7) years, height 177.2 (7.0) cm, body mass 68.9 (16.9) kg) from the Great Britain short-track speed skating (n = 10) and biathlon teams (n = 4) were studied. Each athlete completed a laboratory based and sport specific exercise challenge as well as an EVH challenge, in randomised order.

Results: All 14 athletes completed each challenge. Two had a previous history of asthma. Ten (including the two with a previous history) had a positive test to at least one of the challenges. Ten athletes had a positive response to EVH; of these, only three also had a positive response to the sport specific challenge. No athletes had a positive response to the laboratory based challenge.

Conclusions: Elite athletes should be screened for EIA. EVH is a more sensitive challenge in asymptomatic athletes than sport specific and laboratory based challenges. If sporting governing bodies were to implement screening programmes to test athletes for EIA, EVH is the challenge of choice.

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Accepted 5 September 2005

Exercise induced asthma (EIA) is defined as a transient narrowing of the airways, limiting expiration, following a bout of exercise, which is reversible by inhalation of β_2 agonists.[1] The reported prevalence of EIA in winter athletes ranges from 9% to 50%,[2] which is higher than that of the general population (approximately 8% in the United Kingdom), but in line with estimates for elite summer sports athletes.[3]

At both the 2002 Salt Lake City Winter Olympics and the 2004 Athens Summer Olympics, athletes who wished to use inhaled β_2 agonists therapeutically were required to provide evidence of asthma through bronchodilator or bronchial provocation challenges. At present, there is no gold standard test for EIA; however, the International Olympic Committee-Medical Commission (IOC-MC) accepts the results of various different airway challenges, including exercise, eucapnic voluntary hyperventilation (EVH), methacholine, and saline challenges.[4]

Exercise is an indirect airway challenge that has a high level of specificity,[4] but its sensitivity is affected by environmental conditions.[5] Accordingly, exercise challenges in sport specific environments are more sensitive than challenges conducted in laboratory settings.[5] This is probably because the air conditioned laboratory environment has a relatively high temperature (around 20°C) and water content (around 50% relative humidity). Airway drying[6–10] and airway cooling[7 11 12] have been proposed as mechanisms in the aetiology of EIA. Therefore an air conditioned laboratory based environment may not be sufficiently provocative, especially for winter athletes, who train and compete at sub-zero temperatures, where the water content of the air is very low. Despite this, laboratory based exercise challenges are still used to test elite athletes for EIA.

Eucapnic voluntary hyperventilation (EVH) is a laboratory based indirect airway challenge that enables minute ventilation and environmental conditions to be controlled. The EVH challenge has been reported to be the most suitable method for diagnosing EIA in cold weather athletes.[13 14] However, over half the requests for therapeutic use exemption for β_2 agonists submitted for the 2002 Salt Lake City Winter Olympics employed direct airway challenges to establish EIA (that is, methacholine and histamine).[4] The sensitivity and specificity of these methods have been challenged. Holzer *et al*[10] screened 50 athletes for EIA using methacholine and EVH challenges and found that only nine athletes (18%) had a positive challenge to methacholine, whereas 25 (50%, including the nine methacholine positive athletes) had a positive EVH challenge. The investigators concluded that an EVH challenge was more sensitive and specific than a methacholine challenge for the diagnosis of EIA in athletes. Thus evidence suggests that direct airway challenges are not sufficiently sensitive or specific for use in athletes.

Owing to the lack of sensitivity and specificity of symptom based diagnosis[15] and direct airway challenges,[10] several groups have recently suggested that athletes should be screened for EIA using either EVH challenge or exercise challenges.[3 16–21] Our aim in this study was to establish the efficacy of screening for EIA and examine the role of the EVH challenge and laboratory based and sport specific exercise challenges in the evaluation of elite winter athletes.

METHODS

Following ethical approval from Harrow local research ethics committee, 14 athletes (mean (SD) age 22.6 (5.7) years, height 177.2 (7.0) cm, weight 68.9 (16.9) kg) from the Great

Abbreviations: EIA, exercise induced asthma; EVH, eucapnic voluntary hyperventilation; FEF_{50}, forced expiratory flow at 50% of forced vital capacity; FEV_1, forced expiratory volume in one second; FEV_1%, FEV_1 as a percentage of forced vital capacity; FVC, forced vital capacity; IOC-MC, International Olympic Committee-Medical Commission; PEF, peak expiratory flow

Table 1 Athlete responses to each challenge

Athlete	Baseline FEV_1 (litres)	% predicted FEV_1	SS ΔFEV_1 (%)	LB ΔFEV_1 (%)	EVH ΔFEV_1 (%)
1	**4.8**	**104**	**−13.9**	**−7.5**	**−20.3**
2	4.0	126	−2.5	1.2	−8.8
3	**4.5**	**113**	**−20.7**	**1.02**	**−35.8**
4	**4.5**	**104**	**−3.4**	**−3.4**	**−11.0**
5	**4.5**	**96**	**−1.1**	**−0.4**	**−14.0**
6*	**4.8**	**100**	**−14.7**	**−7.4**	**−11.8**
7	**4.0**	**113**	**−2.5**	**2.2**	**−10.8**
8	4.1	97	2.4	−1.4	−3.4
9	4.0	114	−7.2	−3.18	−3.5
10*	**3.6**	**79**	**−9.1**	**−1.7**	**−12.5**
11†	**4.7**	**104**	**−4.1**	**0.2**	**−11.4**
12†	5.1	104	−8.2	−8.8	−4.7
13†	**5.1**	**120**	**−2.9**	**3.3**	**−18.4**
14†	**4.1**	**96**	**−1.5**	**2.4**	**−23.7**
Mean (SD)	4.4 (0.4)	105 (11.8)	−6.4 (6.4)	−1.8 (3.7)	−13.6 (8.7)

EIA positive athletes identified in bold.
*Past history of asthma and regular treatment with beclomethasone or salbutamol.
†Member of the British biathlon team.
EIA, exercise induced asthma; EVH ΔFEV_1, change in forced expiratory volume in one second (FEV_1) following eucapnic voluntary hyperventilation challenge; LB ΔFEV_1, change in FEV_1 following laboratory based exercise challenge; SS ΔFEV_1, change in FEV_1 following sport specific exercise challenge.

Britain short-track speed skating (n = 10) and biathlon teams (n = 4) volunteered to participate, providing written informed consent.

Each athlete completed a laboratory based challenge, a sport specific challenge, and a eucapnic voluntary hyperventilation challenge (EVH) in random order. If an athlete was using asthma medication they were instructed to stop the drug before each test (inhaled corticosteroids, three days before; inhaled long acting β_2 agonist, two days before; inhaled short acting β_2 agonist, on the day of the test).

Laboratory based exercise challenge

The laboratory based challenge required the athlete to run continuously on a treadmill for eight minutes (temperature 18°C, relative humidity (RH) 56%). Exercise intensity was set to elicit a heart rate of more than 90% of maximum (HR_{max}) for the final four minutes of exercise.[22]

Sport specific exercise challenge

The sport specific challenge for the speed skaters involved skating for six minutes (pace ranging between 11 and 12 seconds per 250 m lap) on the ice rink (temperature 8°C, RH 35%). The sport specific challenge for the biathletes involved a 20 minute simulated race in Vaukati, Finland (temperature 1–2°C, RH 31–34%).

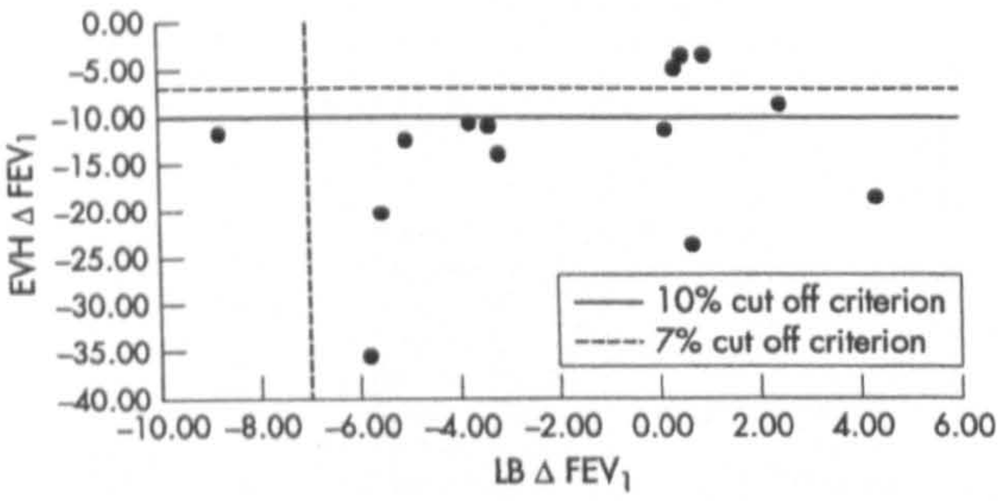

Figure 1 Changes in forced expiratory volume in one second (ΔFEV_1) for each athlete during laboratory based challenge (LB) compared with eucapnic voluntary hyperventilation (EVH). The 7% cut off criterion has been added to show the number of additional athletes who might have received a diagnosis of exercise induced asthma had this criterion been used for exercise challenges.

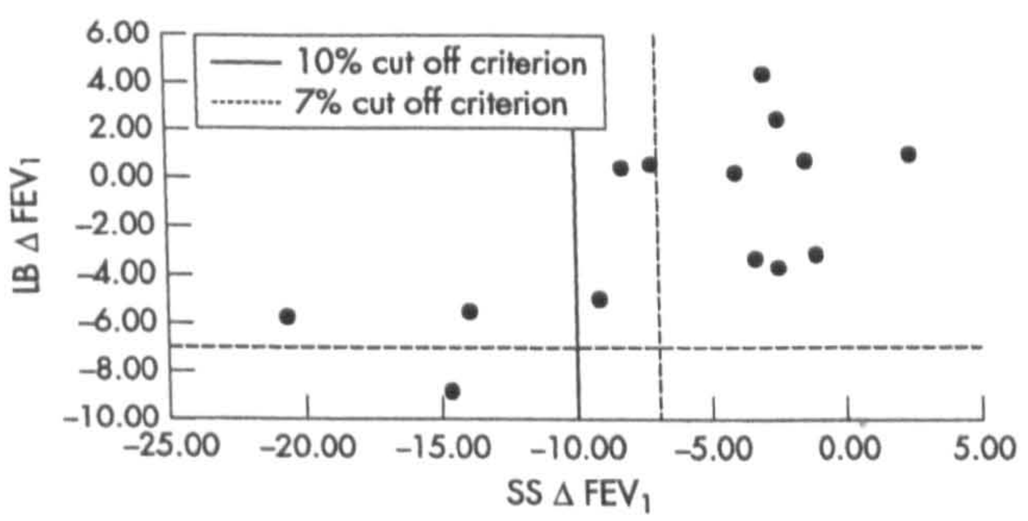

Figure 2 Changes in forced expiratory volume in one second (ΔFEV_1) for each athlete during sport specific challenge (SS) compared with laboratory based challenge (LB). The 7% cut off criterion has been added to show the number of additional athletes who might have received a diagnosis of exercise induced asthma had this criterion been used for exercise challenges.

Eucapnic voluntary hyperventilation

The EVH challenge was conducted in the laboratory and required each athlete to hyperventilate for six minutes (30× baseline forced expiratory volume in one second (FEV_1)), breathing a gas mixture containing 5% CO_2, 21% O_2, and 74% N_2 (inspired air temperature 19.1°C, RH >2%).[23]

A MicroLab ML3500 spirometer (Micro Medical, Rochester, Kent, UK) was used to collect all spirometry measurements. Maximum effort voluntary flow–volume loops were measured before and at 3, 5, 10, and 15 minutes after stopping each challenge. FEV_1, peak expiratory flow (PEF), forced vital capacity (FVC), forced expiratory flow at 50% of FVC (FEF_{50}), and FEV_1 as a percentage of FVC (FEV_1%) were recorded at each time point.

The percentage change (Δ) in FEV_1, PEF, FVC, FEF_{50}, and FEV_1% were calculated for each challenge by taking the lowest value recorded in the 15 minutes following each challenge and expressing the difference between this and the baseline value measured immediately before each challenge as a percentage. A fall in FEV_1 of 10% or more from the baseline value was deemed positive for EIA.

Statistical analysis

Repeated measure analysis of variance (ANOVA) tests were used to compare the changes in ΔFEV_1, ΔPEF, ΔFVC, ΔFEF_{50}, and ΔFEV_1% for each challenge. Planned unpaired *t* tests were used to analyse the difference between positive and

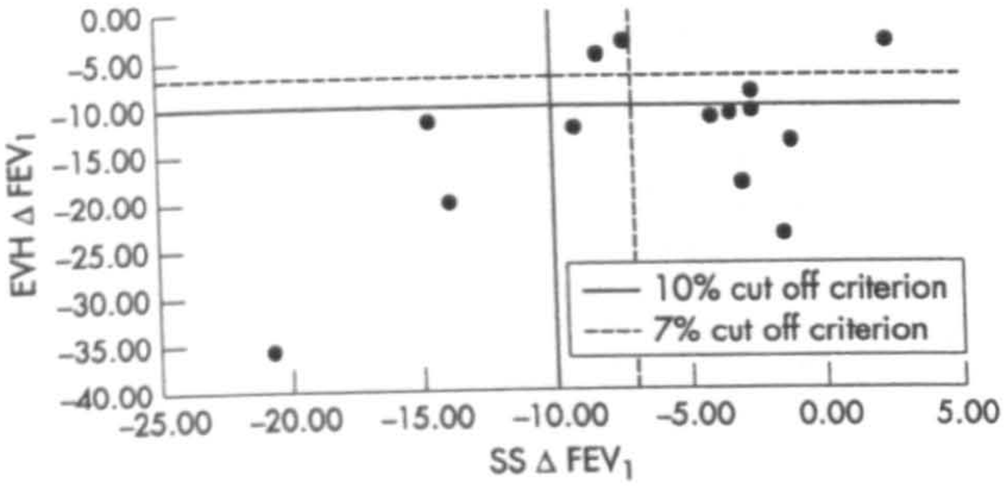

Figure 3 Changes in forced expiratory volume in one second (ΔFEV_1) for each athlete during sport specific challenge (SS) compared with eucapnic voluntary hyperventilation (EVH). The 7% cut off criterion has been added to show the number of additional athletes who might have received a diagnosis of exercise induced asthma had this criterion been used for exercise challenges.

negative athletes for each challenge. A probability (p) value of <0.05 was regarded as significant. All values are presented as mean (SD).

RESULTS

All 14 athletes completed every challenge. Of the 14 athletes, two had a previous history of asthma and were currently treated with beclomethasone and salbutamol inhalers. Baseline lung function and ΔFEV_1 for each challenge are reported for every athlete in table 1.

Based on a $\geqslant$10% fall in FEV_1, 10 of the 14 athletes (including two athletes with a previous history of asthma) had a positive response to at least one of the challenges (table 1). There was no significant difference between baseline FEV_1 predicted values between athletes with positive EIA (102.9 (11.43)%) and negative EIA (110.25 (12.61)%). Ten athletes had a positive response to EVH; of these, only three also had a positive response to the sport specific challenge. No athletes had a positive test to the laboratory based challenge (figs 1–3).

After the assumption of sphericity was met, repeated measures ANOVA showed that ΔFEV_1, ΔPEF, ΔFEF_{50}, and ΔFEV_1% changes were significantly greater ($p<0.05$) following EVH than either the laboratory based or sport specific challenge. The average reductions for EIA positive (ΔFEV_1 $\geqslant$10% for at least one challenge) and EIA negative athletes following laboratory based, sport specific, and EVH challenges are reported in table 2.

DISCUSSION

Our study suggests that screening elite athletes for EIA appears warranted. In addition to the two athletes who had a previous history of EIA, screening elite athletes resulted in the identification of eight others with no history of EIA who had significant bronchial hyperresponsiveness (>10% fall in FEV_1). We have therefore highlighted the findings from previous studies that suggest that many athletes fail to report or to recognise symptoms of EIA.[3 15–17]

Our study showed that the EVH challenge resulted in a greater number of athletes presenting with bronchial hyperresponsiveness commensurate with a diagnosis of EIA than either a sport specific or a laboratory based exercise challenge. Our results are similar to studies that have compared exercise and EVH challenges[13 14] and suggest that the EVH challenge provides a more sensitive diagnosis of EIA in elite winter athletes than the other routinely used non-pharmacological challenges. In our study all athletes who presented with EIA did so through the EVH challenge. In contrast, Rundell *et al*,[14] studying 19 winter athletes with EIA, found that two had a positive exercise challenge but did not have a positive response to EVH. Had our study recruited a larger number of athletes we might have found that EVH did not identify all athletes with EIA. Nevertheless it is clear that EVH is a sensitive and specific challenge for EIA in elite athletes.

The superiority of the EVH challenge results primarily from the greater degree of control over the two main contributors to the airway response—the inspired air water content and minute ventilation. The enhanced control over the condition of the inhaled air and breathing rate during the EVH challenge allows greater confidence that the airways are being adequately stimulated to trigger bronchoconstriction in susceptible subjects.

In line with the greater control of inspired air water content during the EVH challenge, findings from the present study are consistent with the hyperosmolarity theory[6–10] rather than the airway rewarming theory[7 11 12] of EIA development. Despite the colder inspired air temperature during the sport specific challenge (1℃ biathlon, 8℃ speed skating) compared with the laboratory based challenge (18℃), only a three athletes had a positive response. The EVH challenge, which had the largest number of positive tests (10 athletes), was conducted with inspired air temperatures (19.1℃) similar to those of the laboratory based challenge; however, the relative humidity of the inspired air (<2%) was much lower than either the laboratory based (~60%) or the sport specific challenge (31–35%). The

Table 2 Comparison of mean percentage changes for EIA positive and EIA negative athletes for the eucapnic voluntary hyperventilation and sport specific challenges

		LB		SS		EVH	
		No	Δ	No	Δ	No	Δ
FEV_1*†	Positive	0		3	−16.4 (3.73)	10	−16.9 (7.99)
	Negative	14	−1.83 (3.73)	11	−3.6 (3.39)	4	−5.1 (2.51)
PEF*	Positive	0		3	−14.4 (4.38)	10	−14.9 (7.49)
	Negative	14	−2.32 (4.39)	11	−2.9 (5.87)	4	−7.08 (7.09)
FVC	Positive	0		3	−7.7 (2.08)	10	−3.1 (3.37)
	Negative	14	−2.44 (2.26)	11	−3.9 (4.00)	4	−1.7 (2.59)
FEF_{50}†	Positive	0		3	−24.6 (3.79)	10	−30.7 (10.13)
	Negative	14	−2.44 (13.38)	11	−2.9 (17.90)	4	−14.2 (9.93)
FEV_1%*†	Positive	0		3	−9.5 (2.17)	10	−14.4 (6.56)
	Negative	14	0.65 (3.96)	11	0.4 (4.09)	4	−3.41 (2.69)

*Significant difference ($p \leqslant 0.05$) between positive and negative responses following sport specific challenge.
†Significant difference ($p \leqslant 0.05$) between positive and negative responses following eucapnic voluntary hyperventilation.
FEF_{50}, forced expiratory flow at 50% of forced vital capacity; FEV_1, forced expiratory volume in one second; FEV_1%, FEV_1 as a percentage of forced vital capacity; FVC, forced vital capacity; PEF, peak expiratory flow.

provocative nature of dry air inhalation, rather than cold air, lends support to the notion that the underlying mechanisms EIA are not temperature related.

The smaller number of athletes who presented with EIA following sport specific and laboratory based challenges may be because the required 10% fall in FEV_1 is not sensitive enough to detect EIA following laboratory based or sport specific challenges. Work by Helenius *et al*[18 24] has suggested that the 10% cut off criterion for FEV_1 may be insufficiently sensitive to detect EIA in elite athletes and it is not statistically justified. They suggested a fall in FEV_1 of 6.5% as a suitable cut off criterion for elite runners, while Rundell *et al*[5] suggested 7.1%. These values were based on the 95th centile (defined as two standard deviations) of the post-exercise decline in FEV_1 observed in a non-asthmatic population.

In line with Rundell *et al*,[5] a reduction in the cut off criterion to ΔFEV_1 of 7% in the present study resulted in a further two athletes being classified as positive in the sport specific challenge, and four in the laboratory based challenge (figs 1 and 2). No false negative responses were observed. Further work is required to establish standardised cut off criteria for the decline in FEV_1 following various challenges. This may show that the criterion for exercise challenges should be lower than that for an EVH challenge ($FEV_1 \geqslant -10\%$).

In conclusion, our observations support the role of screening elite athletes for EIA and suggest that EVH is a more sensitive challenge for the detection of EIA in asymptomatic athletes than either sport specific or laboratory based challenges. Thus if sporting governing bodies were to implement screening programmes to test athletes for EIA our recommendation is that EVH should be the challenge of choice.

ACKNOWLEDGEMENTS

We are grateful to the European Olympic Committee, UK Sport, British Olympic Medical Trust and Micro Medical Ltd. (www.micro-medical.co.uk)

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Competing interests: none declared

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COMMENTARY

Although this work is not novel, it does confirm and support previous studies evaluating the efficacy of eucapnic voluntary hyperventilation (EVH) as a tool for identifying exercise induced asthma. Previous studies have made similar comparisons with similar results (that is, it is quite well established that a laboratory challenge at room temperature and 50% relative humidity is not an appropriate provocative challenge). The study design is clear and the results solid, although a larger number of subjects would strengthen the study power. An important point to consider is whether or not small falls in FEV_1 (~10%) are of functional significance (in other words, do these small falls affect competition outcomes?); nonetheless, the IOC has set the liberal cut off criterion of a 10% fall in FEV_1. It is important to note that because of to the potency of EVH, only qualified laboratories with appropriate rescue plans in place should entertain its use.

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ASTHMA

Mid-expiratory flow versus FEV_1 measurements in the diagnosis of exercise induced asthma in elite athletes

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Thorax 2006;61:111–114. doi: 10.1136/thx.2005.046615

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Received 12 May 2005
Accepted 14 September 2005
Published Online First 16 October 2005

Background: A fall in FEV_1 of ≥10% following bronchoprovocation (eucapnic voluntary hyperventilation (EVH) or exercise) is regarded as the gold standard criterion for diagnosing exercise induced asthma (EIA) in athletes. Previous studies have suggested that mid-expiratory flow (FEF_{50}) might be used to supplement FEV_1 to improve the sensitivity and specificity of the diagnosis. A study was undertaken to investigate the response of FEF_{50} following EVH or exercise challenges in elite athletes as an adjunct to FEV_1.

Methods: Sixty six male (36 asthmatic, 30 non-asthmatic) and 50 female (24 asthmatic, 26 non-asthmatic) elite athletes volunteered for the study. Maximal voluntary flow-volume loops were measured before and 3, 5, 10, and 15 minutes after stopping EVH or exercise. A fall in FEV_1 of ≥10% and a fall in FEF_{50} of ≥26% were used as the cut off criteria for identification of EIA.

Results: There was a strong correlation between ΔFEV_1 and ΔFEF_{50} following bronchoprovocation ($r = 0.94$, $p = 0.000$). Sixty athletes had a fall in FEV_1 of ≥10% leading to the diagnosis of EIA. Using the FEF_{50} criterion alone led to 21 (35%) of these asthmatic athletes receiving a false negative diagnosis. The lowest fall in FEF_{50} in an athlete with a ≥10% fall in FEV_1 was 14.3%. Reducing the FEF_{50} criteria to ≥14% led to 13 athletes receiving a false positive diagnosis. Only one athlete had a fall in FEF_{50} of ≥26% in the absence of a fall in FEV_1 of ≥10% ($\Delta FEV_1 = 8.9\%$).

Conclusion: The inclusion of FEF_{50} in the diagnosis of EIA in elite athletes reduces the sensitivity and does not enhance the sensitivity or specificity of the diagnosis. The use of FEF_{50} alone is insufficiently sensitive to diagnose EIA reliably in elite athletes.

Exercise induced asthma (EIA) occurs in approximately 90% of chronic asthmatics[1] and has previously been reported to occur in 7–50% of athletic individuals.[2–6] Asthmatic elite athletes currently require evidence of asthma to obtain a therapeutic use exemption certificate which enables them to use therapeutic doses of inhaled β_2 agonists in and out of competition.[7] EIA has previously been diagnosed by a number of challenge methods including exercise,[8 9] eucapnic voluntary hyperventilation (EVH),[10 11] methacholine,[12 13] histamine,[14] saline,[15] and mannitol.[16 17] The International Olympic Committee's Medical Commission (IOC-MC) considers positive tests from exercise, EVH, saline, histamine, and methacholine challenges as evidence of EIA. Methacholine and histamine, however, have been shown to be less specific than exercise for EIA diagnosis.[16 18 19] Exercise and EVH challenges are regarded as the most specific methods of diagnosing EIA in elite athletes.[11]

In all EIA tests recognised by the IOC-MC, forced expiratory volume in 1 second (FEV_1) is the parameter by which changes in maximal expiratory function are assessed, but no "gold standard" methodology exists for athletes or non-athletes.[20] Previous studies that have used FEV_1 to diagnose EIA have suggested using falls in FEV_1 ranging from 7% to 20% as cut off criteria.[21–23] The work carried out by Helenius *et al*[23] suggests that a fall of 10% in FEV_1 following an exercise test is not sensitive enough to diagnose EIA in elite athletes. Despite the absence of a "gold standard" methodology for diagnosing EIA in athletes, the IOC-MC has ruled that an exercise or EVH challenge is positive for EIA when the FEV_1 falls ≥10% from the baseline measurement.

It is possible that the addition of other measurements of expiratory lung function may provide greater sensitivity in the diagnosis of EIA. For example, forced expiratory flow between 25–75% of vital capacity (FEF_{25-75}) has been used in conjunction with FEV_1 to aid the diagnosis of EIA in children[24 25] and athletes.[8 26] Implicitly, FEV_1 measures expiratory flow at high and mid lung volumes, whereas FEF_{25-75} and forced expiratory flow at 50% of vital capacity (FEF_{50}) are markers of expiratory flow through middle lung volumes. It has been suggested that FEF_{25-75} and FEF_{50} are more sensitive to airway obstruction in the small airways than FEV_1.[27 28] Custovic *et al*[24] noted that cut off points for EIA in children (defined as the normal group mean value −2 SD) occurred with a fall in FEV_1 of >10% and a fall in FEF_{25-75} of >26%. In this study, the combined application of FEV_1 and FEF_{25-75} criteria enabled detection of all subjects with EIA. Furthermore, using both FEV_1 and FEF_{25-75} criteria, none of the subjects with allergic rhinitis or dermatitis presented with EIA. The fall in FEV_1 after exercise in children with allergic rhinitis was within the normal range (<2SD), but with a significantly lower mean value than control subjects. The study by Custovic *et al*[24] therefore provides promising evidence to support the addition of mid expiratory flow rates to FEV_1 in the diagnosis of EIA in children that might also be applied to elite athletes. FEF_{50} and FEF_{25-50} measurements are highly correlated and the ratio of the two is reasonably constant. Based on this finding, Bar-Yishay *et al*[29] suggested that reporting both measurements is unnecessary, and they suggested that FEF_{50} should be the preferred measure. This preference was based on the argument that FEF_{50} is easily and directly determined while FEF_{25-50} is a calculated

Abbreviations: EIA, exercise induced asthma; EVH, eucapnic voluntary hyperventilation; FEF_{50}, forced expiratory flow at 50% of vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

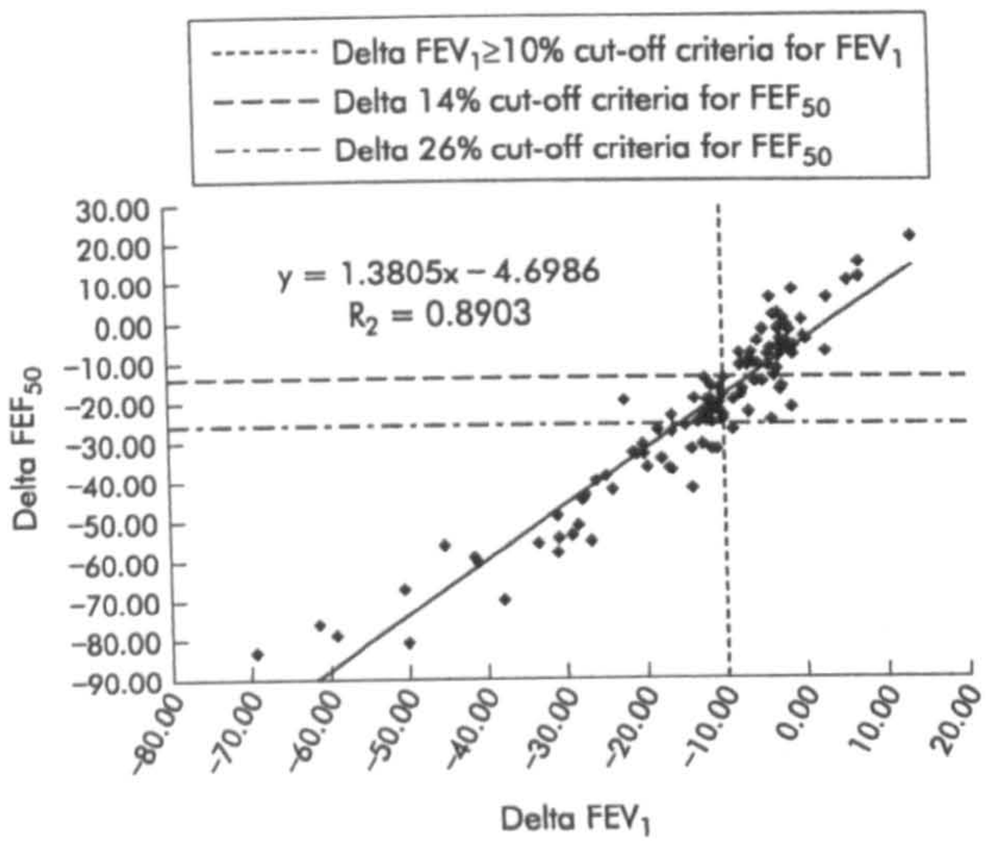

Figure 1 Delta FEV_1 versus delta FEF_{50}.

parameter that is affected by the spirometer manufacturer's choice of algorithm.

The purpose of the present study was to examine the role of FEF_{50} as an adjunct to FEV_1 in the diagnosis of EIA in elite athletes following a bronchoprovocation challenge.

METHODS

Following ethical approval from Harrow local research ethics committee, 66 male elite summer and winter athletes of mean (SD) age 25.1 (4.9) years, height 180.7 (7.8) cm, body mass 77.3 (12.5) kg and 50 female elite athletes of mean (SD) age 24.3 (5.4) years, height 168.2 (7.9) cm, and body mass 62.6 (9.9) kg who held either a Gold or Silver British Olympic Association passport (indicating current or potential Olympic competitive standard) provided written informed consent and volunteered for the study. Of the athletes who participated in this study, 83 had a previous diagnosis of EIA and where using asthma medication. The other 33 athletes had reported symptoms of EIA to a sports physician who had referred them to be tested for EIA. The testing took place at the Olympic Medical Institute, Harrow between June 2003 and June 2004. Athletes were tested at least 2 weeks after a respiratory infection and at least 12 hours following a training session.

Each athlete completed either an exercise or EVH challenge. Exercise challenges involved exercising at an intensity of >85% of maximal heart rate for 6–10 minutes in a sport-specific environment.[30] EVH challenges consisted of hyperventilating for 6 minutes at a rate of 85% maximal voluntary ventilation (30 × baseline FEV_1). The gas inspired during the EVH challenge was a medical gas containing 21% O_2, 5% CO_2 and 74% N_2.[31] For both exercise and EVH challenges, maximal flow-volume loops were measured before and at 3, 5, 10 and 15 minutes after stopping exercise or EVH using a digital spirometer (MicroLab ML3500, Micro Medical Ltd, Rochester, UK) which met ATS guidelines. The lowest values of FEV_1 and FEF_{50} following either exercise or EVH were recorded and the change was calculated (Δ). A ΔFEV_1 of $\geq -10\%$ and ΔFEF_{50} of $\geq -26\%$ were considered cut off criteria for EIA diagnosis.[24]

Table 2 True and false positive and negative diagnoses based on FEF_{50} cut off value of 26%

True positive	39
True negative	55
Total true	94
False negative	21
False positive	1
Total false	22
Total with EIA	60
Total without EIA	56
Total	116

True positive = ΔFEV_1 of ≥10% and a fall in FEF_{50} of ≥26%.
True negative = ΔFEV_1 of ≥10% and did not have a fall in FEF_{50} of ≥26%.
False positive = ΔFEV_1 of <10% and a fall in FEF_{50} of ≥26%.
False negative = ΔFEV_1 of ≥10% and a fall in FEF_{50} of <26%.

Table 3 True and false positive and negative diagnoses based on FEF_{50} cut off value of 14%

True positive	51
True negative	43
Total true	94
False negative	9
False positive	13
Total false	22
Total with EIA	60
Total without EIA	56
Total	116

True positive = ΔFEV_1 of ≥10% and a fall in FEF_{50} of ≥14%.
True negative = ΔFEV_1 of ≥10% and did not have a fall in FEF_{50} of ≥14%.
False positive = ΔFEV_1 of <10% and a fall in FEF_{50} of ≥14%.
False negative = ΔFEV_1 of ≥10% and a fall in FEF_{50} of <14%.

RESULTS

There was a strong positive correlation between ΔFEV_1 and ΔFEF_{50} following bronchoprovocation ($r = 0.94$, $p = 0.000$). Sixty athletes (52%) had a ΔFEV_1 fall of ≥10% leading to the diagnosis of EIA (fig 1). Using the FEF_{50} criteria alone led to 21 (35%) asthmatic athletes receiving a false negative diagnosis; thus, 39 athletes met both FEV_1 and FEF_{50} criteria. The lowest fall in ΔFEF_{50} in an athlete with a ≥10% fall in FEV_1 was 14.3%. Reducing the FEF_{50} criterion to a ≥14% fall included 13 athletes whose ΔFEV_1 was not ≥10% (mean $\Delta FEV_1 = 5.7$, range −8.9 to −1.5). Only one athlete had a

Table 1 Mean (SD) changes in FEF_{50} and FVC following bronchoprovocation challenge

	FEF_{50} (l/s)		FVC (l)	
	Before	After	Before	After
Asthmatic	3.86 (0.92)	2.39 (0.84)**	4.99 (1.00)	4.45 (1.16)**
Non-asthmatic	4.79 (1.37)	4.43 (1.31)	4.81 (1.03)	4.65 (1.04)

Asthmatic athlete defined as having a ≥10% fall in FEV_1 following bronchoprovocation.
**Significantly different ($p<0.05$) from pre-test value.

Table 4 Effectiveness of FEF_{50} cut off criteria of 26% and 14%

	Cut off 26%	Cut off 14%
Specificity	98	77
Sensitivity	65	85
Predictive value of positive test	98	80
Efficiency	81	81

$\geq$26% fall in FEF_{50} in the absence of a $\geq$10% in FEV_1 ($\Delta FEV_1 = 8.9\%$).

Of the 83 athletes with a previous diagnosis of EIA, 33 failed to develop EIA ($\Delta FEV_1 < 10\%$) following bronchoprovocation challenge. Of the 33 athletes who had been referred for testing but had no previous diagnosis of EIA, 10 athletes presented with EIA following bronchoprovocation.

The values for FEF_{50} and forced vital capacity (FVC) before and after bronchoprovocation challenge are shown in table 1. FEF_{50} ($p = 0.000$) and FVC ($p = 0.000$) were significantly lower after bronchoprovocation in the asthmatic athletes. There was no significant change in FEF_{50} or FVC before and after bronchoprovocation challenge in athletes who did not have a fall in FEV_1 of $\geq$10%.

The specificity, sensitivity, predictive value of positive test and efficiency of FEF_{50} cut off criteria of 26% and 14% are shown in tables 2, 3 and 4, respectively.

DISCUSSION

This study shows that the addition of FEF_{50} reduces the sensitivity of EIA diagnosis following exercise or EVH challenge. Of the 60 athletes who were diagnosed with EIA using IOC-MC criteria of a $\geq$10% fall in FEV_1, 21 (35%) would have received a false negative diagnosis using a combination of FEV_1 and FEF_{50} falls. Furthermore, only one athlete exceeded the criterion for FEF_{50} but not for FEV_1. Our study therefore suggests that FEF_{50} does not improve the diagnosis of EIA in elite athletes using the IOC-MC criteria.

In previous studies, measurements of FEF_{25-75} have been used to supplement FEV_1 in the diagnosis of EIA in children[24 25] and athletes.[8 26] The studies conducted on children have supported the addition of FEF_{25-75} measurements to improve the diagnosis of EIA. It has been suggested that FEF_{25-75} is a more sensitive measure of obstruction in the small airways than FEV_1.[32] Thus, EIA may be a disease that consistently affects the expiratory flow through the small airways. Fonseca-Guedes *et al*[25] noted that only 60% of children with "intermittent" EIA met the criteria for both FEV_1 and FEF_{25-75} compared with 94.4% of children with "severe persistent" EIA. They suggested that FEF_{25-75} is more likely to fall significantly than FEV_1 in children with mild EIA. Our data do not agree with this finding and suggest that FEV_1 is more likely to fall significantly in athletes with mild asthma. Indeed, only one athlete had a significant fall in FEF_{50} ($\geq$26%) in the absence of a significant fall in FEV_1, while 21 athletes had a significant fall in FEV_1 ($\geq$10%) in the absence of a significant fall in FEF_{50}. Only 39 athletes met both criteria for FEF_{50} and FEV_1, which would have resulted in 21 (35%) athletes (who met FEV_1 criteria) receiving a false negative diagnosis for EIA. The reduced sensitivity found following the inclusion of the FEF_{50} measurement suggests that, in elite athletes with mild EIA, expiratory airflow is just as likely to be restricted in the larger airways as in the smaller airways. It is therefore appropriate to assess expiratory flow using an index of function for both the larger and smaller airways of the lung—that is, FEV_1.

A number of studies have examined the diagnosis of EIA in athletes but they have not specifically used mid-expiratory flow rates as a criterion for making the diagnosis. Rundell *et al*[8] suggested that a fall in FEF_{25-75} of 14% is significant in the diagnosis of EIA in winter athletes. This lower limit was calculated by taking the mean post exercise change from baseline spirometry and subtracting 2 standard deviations. Lowering the FEF_{50} cut off value in our data to $\geq$14% resulted in an increase in the sensitivity but a decrease in the specificity from 98% to 77%. Using a 14% cut off value, 13 athletes would have been diagnosed with EIA who did not meet the IOC-MC criterion of a 10% fall in FEV_1 from baseline values.

A further problem associated with the use of FEF_{50} as a criterion measurement is that its reliability is dependent upon the constancy of FVC. Our results show that the mean fall in FEF_{50} following bronchoconstriction was accompanied by a mean fall in FVC in athletes with EIA. The fall in FEF_{50} seen in some of athletes following a bronchoprovocation test may therefore be partially attributable to a reduction in FVC. The reduction in FVC in asthmatic athletes may be due to the prolongation and discomfort associated with exhaling to residual volume during bronchoconstriction. Despite standard controls, this may cause the athlete to stop exhaling before reaching residual volume. This shortcoming further undermines the potential value of FEF_{50} for diagnosing EIA.

In conclusion, the addition of FEF_{50} to FEV_1 reduces the sensitivity of a diagnosis of EIA in elite athletes. Our data suggest that a more global measure of maximal expiratory airflow (FEV_1) provides the most sensitive and specific diagnosis of EIA, especially when the severity of the disease is thought to be mild. This would suggest that EIA is a disease that is associated with expiratory flow limitation in the larger and smaller airways of elite athletes. However, methodological issues associated with assessment of FEF_{50} (reliance upon FVC) mean that this interpretation should be viewed cautiously. The authors suggest that future studies should investigate the efficacy of the IOC-MC criterion of a 10% fall in FEV_1 to define a more statistically justified cut off point for the diagnosis of EIA in elite athletes.

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The authors are grateful to the European Olympic Committee, UK Sport, British Olympic Medical Trust, Olympic Medical Institute, and Micro Medical Ltd.

Competing interests: none declared

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