ASTHMA, EIB AND THE ATHLETE

DIAGNOSIS, PREVALENCE, TREATMENT AND ANTI-DOPING

– Written by Greg Whyte, UK

Asthma is a chronic inflammatory disease of the airways thought to be caused by a combination of genetic and environmental factors with a prevalence of c.7.8% in the general UK adult population with c.300 million people affected worldwide. Asthma is characterised by reversible airflow obstruction, bronchospasm and variable and recurring symptoms including: wheezing, coughing, chest tightness and shortness of breath. The common clinical classification of asthma is based upon the frequency of symptoms, forced expiratory volume in one second (FEV1) and peak expiratory flow rate. Asthma may also be classified as atopic (extrinsic) or non-atopic (intrinsic) where atopy refers to a predisposition toward developing type 1 hypersensitivity reactions (i.e. allergic reaction provoked by re-exposure to a specific allergen).

'Unconditioned air' is air that has not been filtered through the nose or moistened through the upper respiratory tract.

Exercise-induced bronchoconstriction (EIB) is closely related to asthma and is defined as a transient narrowing of the airways, limiting expiration that usually follows a bout of exercise. It is reversible spontaneously or through the inhalation of a short-acting ß$_2$-agonist (e.g. salbutamol). EIB has been estimated to occur in up to 90% of asthmatics and also found in around 10% of people without a known history of asthma. EIB can be triggered by an increase in the volume of 'unconditioned' air inspired through the mouth. During increased

> ***Winter sport athletes generally have a higher prevalence of EIB than those engaged in summer sports***

levels of activity 'unconditioned' air cools and dries the upper and lower airways inducing inflammation and smooth muscle contraction leading to bronchial narrowing that is readily reversible with inhaled short-acting ß$_2$-agonists. Symptoms of EIB are very non-specific, mimicking those of asthma including:

- wheezing,
- dyspnoea,
- cough and
- chest tightness.

Given the lack of specificity, subjective symptoms are usually poorly correlated with objectively documented EIB highlighting the importance of incorporating an objective bronchoprovocation challenge into the diagnosis of EIB. This is particularly true for active individuals where normal physiological responses to exercise may be difficult to differentiate from EIB symptoms.

PREVALENCE OF EIB IN ATHLETES

The prevalence of EIB in athletic populations has been shown to vary between 9 and 55% depending on the type of sport, diagnostic test used and environmental conditions. Winter sport athletes generally have a higher prevalence of EIB than those engaged in summer sports. In summer sport athletes, we observed a significant variation between sports in the prevalence of EIB in Team GB Olympic teams, with swimming having one of the highest at 40%[1]. It has been suggested that the high prevalence of EIB 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 EIB[2]. In winter sport athletes such as figure skaters and cross-country skiers a similarly high prevalence of EIB has been reported (35 and 50% respectively), which has been associated with training and competing in cold and dry and polluted environments[3,4]. This suggests that athletes who compete in certain sports may be more susceptible to the development of EIB than others.

DIAGNOSIS AND SCREENING

A large number of early studies have reported the prevalence of asthma by the sole use of questionnaires and symptoms. This approach is regarded as a poor method of assessment due to its low sensitivity and specificity. For example, Rundell et al[5] examined the accuracy of symptom-based diagnosis compared with an exercise challenge to diagnose EIB in elite winter athletes by comparing results from an asthma symptoms questionnaire with those from an exercise challenge. Of the 26% of participants who tested positive for EIB in response to the exercise challenge, only 40% reported more than one symptom of EIB. Post-exercise cough was the most common symptom reported by both EIB positive and EIA negative athletes.

The high number of false positives and false negatives from questionnaire diagnosis highlights the need for an objective bronchoprovocation test and supports the International Olympic Committee Medical Commission requirement for athletes to produce quantitative evidence of their asthma. Traditionally, exercise challenges have been employed to identify EIB. However, despite the strong ecological validity of these tests, the poor control of effort, ventilation and environment has

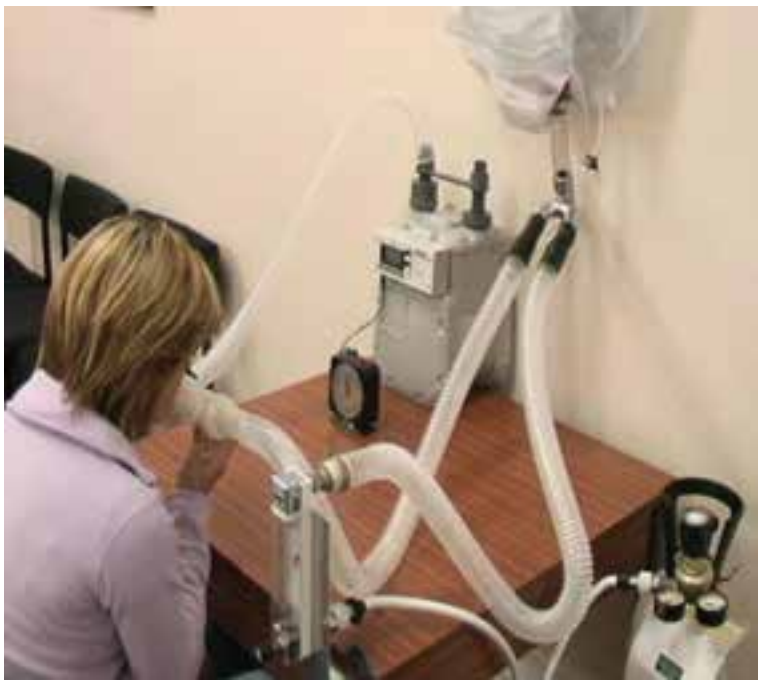

Figure 1: Spirometry assessment of lung function and the Eucapnic Voluntary Hyperpnoea (EVH) challenge.

led to the development of more controlled assessment methods[6].

The EVH Challenge

While a number of bronchoprovocation challenges are currently available e.g. Histamine, Metacholine, Saline and Mannitol, the Eucapnic Voluntary Hyperpnoea (EVH) challenge appears to be the best surrogate for exercise, requiring athletes to achieve a target minute ventilation (VE) of 85% (baseline 30 × FEV1) of their predicted maximal voluntary ventilation rate (MVV) for 6 minutes while breathing dry (<2% relative humidity) air that consists of 21% oxygen, 5% carbon dioxide and 74% nitrogen (Figure 1). The EVH challenge has been shown to possess a high specificity and sensitivity in the diagnosis of EIB in elite athletes and has therefore been adopted by the International Olympic Committee Medical Commission to provide evidence of EIB and the use of inhaled short-acting $ß_2$-agonists during Olympic competition. In addition to ensuring athletes are given appropriate guidance and training to complete a successful EVH challenge, the EVH test is only available in a limited number of specialist centres and requires trained technicians, scientists and medics to optimise its clinical value.

Using objective tests such as EVH, studies have identified a large sub-group of athletes with no previous diagnosis of EIB, who exhibit a positive response to EVH prompting the issue of screening in athletic populations. When elite athletes are screened for EIB, via an EVH challenge, a large number (74%) of the positive challenges come from athletes with no previous history of asthma[7]. This finding can be explained by elite athletes not reporting symptoms or failing to relate exercise related respiratory symptoms (i.e. post exercise cough) with asthma/EIB. There are, however, a number of limitations associated with screening using of EVH in isolation. The EVH challenge is a very provocative test that may elicit airway hyper-responsiveness only with this unique trigger, which is not typical of the environment in which the athlete trains or competes. This may reduce the relevance of the test for these athletes and there may be a need to adjust the cut-off threshold for a positive test or to supplement the test with some form of sport-specific exercise challenge in order to provide a more ecologically valid diagnosis. Furthermore, without measures of airway inflammation it is difficult to state conclusively what is triggering the EIB, which reduces the specificity of the treatment for the athlete.

Best practice in the diagnosis of EIB is achieved when an objective indirect airway challenge accompanies the practitioner's consultation with the patient.

TREATMENT AND ANTI-DOPING REGULATION

Inhaled corticosteroids, long-acting $ß_2$-agonists and leukotriene antagonists are commonly used to control asthma symptoms and chronic airway inflammation (often termed 'preventer' medication). Inhaled short-acting $ß_2$-agonists are commonly used bronchodilators and are essential as 'reliever' therapy in the management of asthma. The principle role of inhaled short-acting $ß_2$-agonists is to act as a bronchodilator to reverse the bronchoconstriction of airway smooth muscle. This results in the asthmatic airway becoming dilated, leading to reduced airway resistance and improvements in minute ventilation ($\dot{V}E$). It has been suggested that inhaled short-acting $ß_2$-agonists may result in a performance improvement by causing a significant bronchodilation in the airways of non-asthmatic athletes leading to an improved $\dot{V}E$, increased oxygen uptake and exercise performance. However, there is limited evidence to suggest that inhaled doses of $ß_2$-agonist (e.g. salbutamol,

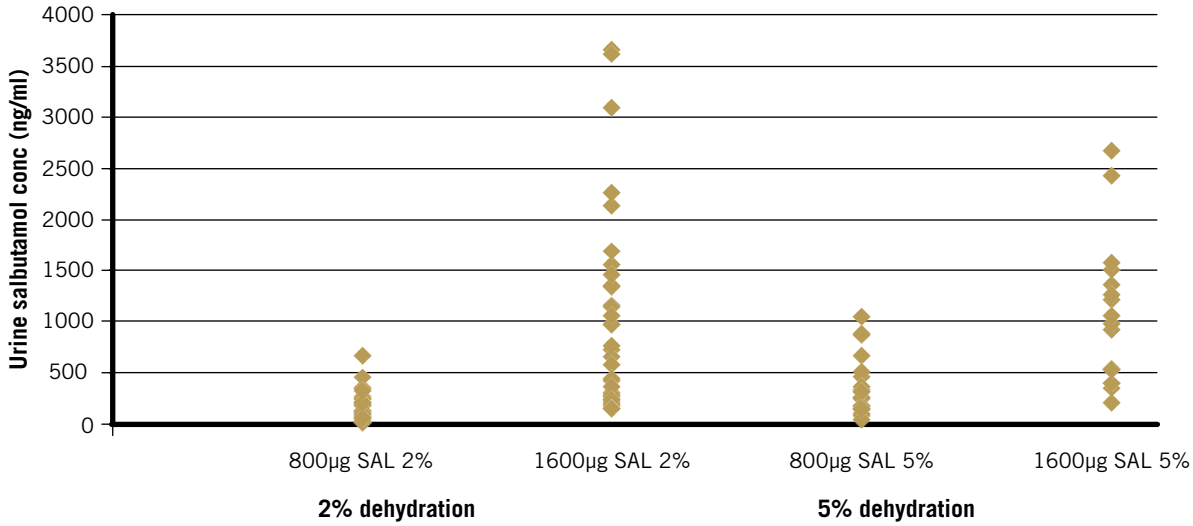

Figure 2: Urine drug concentration following inhalation of 800 µg or 1600 µg salbutamol under dehydration of 2 and 5% of body mass. Results show a number of athletes presenting with positive urine samples above WADA Threshold and Detection Limit.

salmeterol, formoterol) have a significant ergogenic effect. The small numbers of studies that do exist have focussed on endurance performance and have reported no performance effect of up to 800 µg of inhaled short acting ß$_2$-agonist[8]. Recent data from our own lab supports the lack of ergogenic efficacy following the acute and chronic inhalation of the WADA daily upper limit of 1600 µg in endurance and team game performance.

Despite the absence of data supporting an ergogenic effect of short-acting ß$_2$-agonists the use of this class of medication in the treatment of asthmatic athletes is restricted by anti-doping regulations. The origins of these rules can be traced back to the 1972 Munich Olympics when salbutamol was prohibited for the first time. Since then their status has switched from prohibited (1972 to 1975) to permitted with notification before the event (1976 to 1983; 1993 to 2000), permitted with retrospective notification (1984 to 1985), fully permitted (1986 to 1992) and prohibited without a therapeutic use exemption (2001 to 2009)[8]. In January 2010, WADA rules changed again and the use of all short-acting ß$_2$-agonists was prohibited in athletes (both in and out of competition), except for salbutamol and salmeterol by inhalation, which required a declaration of use. In January 2011, the requirement to submit a declaration of use was lifted for salbutamol and salmeterol and these are now permitted by inhalation. In contrast, other short-acting ß$_2$-agonists remain on the restricted list e.g. Terbutaline.

While inhaled salbutamol is now permitted, WADA have set a daily upper limit of 1600 µg (16 puffs of a standard 100 µg inhaler), with recommended dosing regimens between 100 and 400 µg up to four times daily. Furthermore, WADA have set a urinary drug threshold of 1000 ng.ml^{-1} (formoterol: 30 ng/ml; currently no set cut-off limit for salmeterol; WADA, 2012). The purpose of this urinary threshold is to distinguish legitimate therapeutic use from misuse. Based on this recommendation, we recently investigated the impact of inhaling the entire WADA 24-hour limit of 1600 µg of salbutamol in a single dose under euhydrated and dehydrated states. The rationale behind this is that athletes are regularly prescribed salbutamol pro re nata (when required). Individuals encouraged to administer salbutamol 'pro re nata' may overdose above such recommendations, for therapeutic purposes, either intentionally or inadvertently. In such cases athletes are at risk of exceeding the WADA threshold and in doing so, facing possible anti-doping sanctions. Indeed, recently, a Rugby League player in the UK escaped a doping violation after he inhaled over 1600 µg over the course of a match and then tested positive in the post-match anti-doping test. The player's defence was based on the prescription on an 'as needed basis' with no guidance on an upper limit to its use. Accordingly, in practice 16 inhalations in a short period of time prior to [competition] endurance performance may occur in poorly controlled, less-informed, as well as potentially unscrupulous athletes and yet still working within the recommended limit stated on the 2012 Prohibited List. The results of our investigations on behalf of WADA show that inhalation of 1600 µg of salbutamol may result in a positive finding which is exacerbated following dehydration (Figure 2).

> ***Individuals encouraged to administer salbutamol 'pro re nata' may overdose above recommendations and risk exceeding the WADA threshold***

Athletes and support staff should be educated around the use of salbutamol and provide guidelines on what qualifies as misuse (inhaled doses >800 µg) as it may result in salbutamol levels exceeding the 1000 $ng.ml^{-1}$ threshold value and a positive anti-doping violation.

TAKE HOME MESSAGE

Inhaled $ß_2$-agonists have no performance-enhancing effect and the requirement for an objective bronchoprovocation challenge in the diagnosis of EIB, guided by the International Olympic Committee Medical Commission, are based on health not doping (performance-enhancing) concerns. The justification of this is supported by evidence from our lab and others. The poor sensitivity and specificity of symptoms reported by athletes has led to a call for screening, however further data is required before mandatory screening is established. Short-acting $ß_2$-agonists are prescribed for the acute control of EIB, and WADA have set an upper limit for the inhalation of salbutamol at 1600 µg over a 24-hour period. Recent data from our lab has, however, demonstrated that the acute inhalation of a single dose of 1600 µg may result in a doping violation. Accordingly, athletes and support staff should be educated around the appropriate use of asthma medication with a focus on the chronic control of inflammation ('preventer' medication i.e. corticosteroids, long-acting $ß_2$-agonists, leukotriene antagonists) rather than the acute administration of bronchodilators ('reliever' medication i.e. salbutamol, salmeterol, formoterol).

References

1. *Dickinson JW, Whyte GP, McConnell AK, Harries MG. Impact of changes in the IOC-MC asthma criteria: a British perspective. Thorax. 2005; 60:629-632.*
2. *Nemery B, Hoet PH, Nowak D. Indoor swimming pools, water chlorination and respiratory health. Eur Respir J 2002; 19:790-793.*
3. *Rundell KW. Pulmonary function decay in women ice hockey players: is there a relationship to ice rink air quality? Inhal Toxicol 2004; 16:117-123.*
4. *Dickinson JW, Whyte GP, McConnell AK, Nevill AM, Harries MG. Mid-expiratory flow vs. FEV1 measurements in the diagnosis of exercise induced asthma in elite athletes. Thorax 2006; 61:111-114.*
5. *Rundell KW, Im J, Mayers LB, Wilber RL, Szmedra L, Schmitz HR. Self-reported symptoms and exercise-induced asthma in the elite athlete. Med Sci Sports Exerc 2001; 33:208-213.*
6. *Dickinson JW, Whyte GP, McConnell AK, Harries MG. Screening elite winter athletes for exercise induced asthma: a comparison of three challenge methods. Br J Sports Med 2006; 40:179-183.*
7. *Dickinson J, McConnell A, Whyte GP. Diagnosis of exercise-induced bronchoconstriction: eucapnic voluntary hyperpnoea challenges identify previously undiagnosed elite athletes with exercise-induced bronchoconstriction. Br J Sports Med 2011; 45:1126-1131.*
8. *Pluim BM, de Hon O, Staal JB, Limpens J, Kuipers H, Overbeek SE et al. ß2-Agonists and physical performance: a systematic review and meta-analysis of randomized controlled trials. Sports Med 2011; 41:39-57.*
9. *The World Anti-Doping Agency. The 2012 Prohibited List International Standard. From: http://www.wada-ama.org/Documents/World_Anti-Doping_Program/WADP-Prohibited-list/2012/WADA_Prohibited_List_2012_EN.pdf.*

Greg Whyte Ph.D., D.Sc., F.B.A.S.E.S., F.A.C.S.M.

Research Institute for Sport and Exercise Science

Liverpool John Moores University

Liverpool, UK

Contact: gregwhyte27@yahoo.co.uk