Asthma and exercise induced bronchospasm

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ABSTRACT

Exercise induced asthma or bronchospasm (EIA or EIB) is a transient, reversible, and intermittent narrowing of the airways, occurring about 10-15 minutes after intense exercise (aerobic activity more than anaerobic), performed for 8-10 minutes. It affects up to 18% of the general population, depending on reporting methodology, and its documented prevalence among athletes is up to 20%. Many treatments are available, starting with education and prevention, to enable avoidance of possible trigger factors and reduce the exacerbation of symptoms. Pharmacologic agents are useful both for prevention and treatment, even if their use should always be adapted to the individual conditions. For athletes, special care must be taken to integrate any treatment option with the training and competition programme, particularly with regard to anti-doping regulations. IAAF and WADA rules oblige athletes to obtain a diagnosis and/or a therapeutic use exemption before use of some medicines included in the WADA lists of banned substances and methods. This article presents an overview of the current literature on asthma, its treatment and implications for athletes. The aim is to give information and guidance to athletes, their coaches and particularly their medical support.

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Introduction

Asthma is a worldwide problem, with up to 300 million individuals estimated as being affected. Even if different definitions are the reason for disparate reporting in different countries, it appears that the global prevalence varies from 1% to 18% in most populations, and that it has increased in the last 20 years.

Different factors can influence the development and expression of asthma. Individual factors include (A) genetic or familiar predisposition linked both to airway hyper-responsiveness and to response to different treatments; (B) sex related prevalence in males more than in females in younger ages, which seems reversed in adulthood[49]. Environmental aetiological factors include infections, allergens, occupational exposure to external work agents, tobacco smoke, outdoor or indoor pollutants and foods.

As would be expected, expressions of asthma also affect a significant percentage of sportsmen and sportswomen, including athletes. Integrating treatment into training and competition is therefore an issue. Of special concern are the anti-doping implications. Particular limitations by IAAF and WADA anti-doping rules oblige the athletes to obtain a correct and documented diagnosis before treatment and/or to obtain, when requested, a therapeutic use exemption (TUE) for the use of some medicines that are included in the yearly updated WADA lists of banned substances and methods.

This article presents an overview of the current literature on asthma, its treatment and implications for athletes. The aim is to give information and guidance to athletes, their coaches and particularly their medical support.

Definitions

According to the American Thoracic Society, asthma is a clinical lung disease characterised by reversible airway obstruction as a consequence of a wide variety of stimuli. The term *current asthma i*s used when at least one asthmatic episode has occurred during the last year. Asthma is characterised by a variety of symptoms, including dyspnoea, shortness of breath, wheezing, cough, excess mucus, breathlessness, and chest tightness. The symptoms might be mild or severe; intermittent or continuous; and more frequent at night and early in the morning. Upper or lower airway obstructions are reversible with or without therapy. The generic definition can also include *bronchial or airway hyper-responsiveness* (BHR or AHR), that is, an above-normal airway constriction upon exposure to physical stimuli or sensitising agents[53]. A transient airway narrowing occurring in susceptible individuals during or after exercise is defined as EIB *(Exercise Induced Bronchospasm)* when observed in a non-asthmatic and non-atopic population or EIA *(Exercise Induced Asthma)* when including asthmatic individuals[1, 2, 4].

Exercise Induced Asthma or Bronchospasm is a transient, reversible, and intermittent narrowing of small and large airways, occurring about 5-15 minutes after intense exercise (aerobic activity more than anaerobic), performed for 8-10 minutes [3, 28]. A post-exercise fall in forced expiratory volume in one second of >10% is required for diagnosis. After an attack lasting 20-60 minutes, a complete recovery usually occurs. In 50% of affected athletes, a refractory phase starts less than one hour after initial exercise; this may last up to three hours, with less than half intensity of exercise bronchospasm[7]. For this reason, the warm-up period might be useful for athletes, as this makes it possible to ensure a refractory phase during competition. Sometimes, six to eight up to 12 hours after the exercise, a late phase, less severe state with cough and wheezing is observed in 30% of subjects with EIA. The aetiology of the refractory period is probably due to the depletion of local mediators, or increased sympathetic activity[5].

EIA occurs in 12-15% up to 20-25% of the normal population, increasing to 35-40% in subjects with allergic rhinitis or hay fever and/or eczema, and up to 90% of those with asthma. The variability of the statistical data depends mainly on the method used (clinical or laboratory evaluation or epidemiologic questionnaires based on self-reported symptoms or statistics performed in main competitions, based also on declared use of beta-2 agonists). The prevalence of BHR (bronchial hyperreactivity), evaluated by methacholine in competitive athletes of various sports appears double when compared with sedentary subjects and is higher in athletes exercising in cold air, dry air, humid air and a combination of all [6, 8].

Recently, ANDERSON et al.[10,15] and FITCH[14] reported that 5.2% of all participating athletes during 2002 Winter Olympic Games and 4.2% of participating athletes during 2004 Summer Olympics inhaled beta-2 agonists, after application for their use. FITCH, from data collected over three summer Olympic Games, (Atlanta 1996, Sydney 2000 and Athens 2004) observed the largest use, up to 15.4% in some particular disciplines and in endurance sports, mainly cycling, triathlon and swimming[13]. Gen-

erally the prevalence was higher in winter than in summer sports, and in endurance athletes, more than in other disciplines[9, 11, 12]. Different studies, performed in various countries on elite athletes participating in the Olympic Games, showed different prevalence of BHR, sometimes up to 21-23%, with positive bronco provocation tests.

Aetiology

Sometimes, EIA is erroneously diagnosed in athletes who have respiratory stridor during inspiration, typical of vocal cord dysfunction (VCD) or exercise-induced inspiratory stridor, prevalent in young female athletes, statistically up to 5%, associated, paradoxically, with narrowing of the vocal cords during inspiration or as described by patients, while "getting air in" [17, 39].

Swimming-induced pulmonary oedema (SIPE) should be differentiated from EIA. This condition, sometimes reported in swimmers after heavy training session, with transient restrictive pulmonary function lasting up to one week, is not typical in track & field[19].

Other upper respiratory disorders, anxiety and hyperventilation syndrome may mimic asthma or EIA. Psychological disturbance, connected with poor training and/or performance impairment, may be, in particular conditions, erroneously attributed to hypothetic airways constriction[20].

EIA is more prevalent in female athletes, and twice as prevalent in endurance athletes as in sprinters, jumpers and throwers in track and field. Furthermore, evidence exists that top athletes are at an increased risk of developing asthma or EIA in their career, particularly in endurance events. High-level exercise performed on a regular basis by previously unaffected elite athletes, particularly in endurance activities, is liable to increase the incidence of asthma and airway hyper-responsiveness (AHR)[23].

A basic genetic component associated with atopy is presupposed[31]; allergic rhinitis, often associated with conjunctivitis, with higher prevalence in athletes (up to 48-50%), was observed in some sports, with consequent higher BHR and incidence of EIA; but other mechanisms, independent of allergen exposure, cannot be excluded, as shown by the presence of cold-induced rhinitis in skiers[16].

Many other factors are involved and play a significant role both in asthma and AHR; particularly in athletes[22] these include:

1. **Recurrent airway infections or inflammations**, in which many local cells and their related mediators are involved (mast cells, macrophages, eosinophils, neutrophils, etc). Increased levels of neutrophils and eosinophils both in serum and in sputum are also frequently observed after training and competition in non-asthmatic athletes, even without standard higher levels in hyperresponsive or asthmatic athletes with EIB or EIA. Endurance athletes are particularly susceptible to upper respiratory tract infection and impaired function of the immune system after intense repeated training, with decreased activity of lymphocytes, neutrophils, macrophages, and natural killer (NK) cells and diminution of lymphokines and IgA levels [24, 25].

2. **Allergies** including drug allergy (aspirin or FANS are common), food allergy, or other allergic or anaphylactic medical conditions[21, 44]. Also, exercise-induced anaphylaxis, sometimes supposed as been connected with food allergy, might be involved with the suffered exercise induced bronchospasm[18].

3. **Environmental exposure to airborne allergens**. Prolonged hyperventilation during intense training increases the possibility of exposure to different allergens, mainly in seasonal asthmatic patients. These include pollens or other allergen, or irritant pollutants such as cigarette smoke and sulphur dioxide (SO_2), carbon monoxide (CO), nitrous and nitric oxide (NO_2 - NO_3) in smog, and - very important in track and field - also herbicides, pesticides, insecticides, and fertilisers[32]. Similarly, ultrafine particulate in indoor ice rinks are demonstrated as trigger factors[34]. Training sessions in contaminated situations can cause chronic

bronchial inflammation triggered by smoke, pollens, irritants, and allergens (IgE production)[26]. Similarly, exposure to chlorinated compounds might have adverse effects in competitive swimmers [30, 33].

4. **Hyperventilation and cold or dry air inhalation.** First of all, bronchial constriction might be directly elicited by airway cooling via reflex stimulation of tracheo-bronchial receptors. The same vasoconstriction by cold air might induce secondary hyperaemia, with oedema and airway constriction. Furthermore, increased ventilation during exercise normally induces vapour loss, due to the different relative humidity inside the bronchial system and in external air, reducing water in the bronchial membranes and increasing the osmolarity, with consequent release of mediators; this mechanism, mainly during endurance efforts and/or in cold or dry air conditions, induces a loss of heat and water in the bronchial system: the bronchoconstriction response is due both to the direct effect of "cooling" in bronchial mucosa by airways receptors stimulation, and to the "hyperosmolarity" of mucosal fluid, inducing the release of pro-inflammatory mediators (histamine, leukotrienes, prostaglandins, neutrophil chemiotactic factors). In addition, the "rewarming" after exercise generates a vasodilator effect, a kind of reactive hyperaemia on the pulmonary capillary system with vascular bronchial congestion, increased vascular permeability and oedema with bronchoconstriction. Sometimes, not only airway cooling, but also hot dry air may exitate in severe bronchoconstriction or altered bronchovascular permeability[27, 35, 36].

5. **Parasympathetic hyperactivity** is a typical compensatory response to a prolonged sympathetic stimulation by intense and prolonged training sessions, which may increase the bronchomotor tone (normally and basically the parasympathetic system is dominant over the sympathetic system in the bronchial apparatus), and may explain the higher incidence of AHR in endurance athletes; similarly to the increased vagal bronchomotor tone typical of night or early morning hours, which is the reason of easier onset of bronchoconstriction attacks in asthmatic subjects in this period of the day [29, 40].

Clinical Diagnosis

1. Self-reported symptoms are usually not valid to confirm the presence of asthma or EIA. Too many athletes refer respiratory symptoms without suffering bronchial asthma or EIA. The misinterpretation of post-exercise fatigue, prolonged recovery time, under-performances, or inadequate training might induce an erroneous diagnosis [37, 38].

2. History and clinical evaluation are very important, and permit, as a first step, the evaluation of exercise related symptoms (EIA or EIB) and/or allergy and discrimination of other possible diseases:
- Chronic bronchitis, pulmonary fibrosis, lymphoadenopathy;
- Seasonal asthma;
- Infectious diseases;
- Laryngeal dysfunction; throat or nasal problems; upper airways obstruction;
- Allergic rhinitis; hypertrophic turbinates; nasal polyps; sinusitis; hay fever;
- Cardiac problems with effort dyspnoea;
- Allergic conditions (medicines, food) or anaphylactic reactions;
- Blood disorders (anaemia);
- Thyroid dysfunction;
- Gastro-oesophageal reflux;
- Anxiety.

3. Basal screening is carried out with many clinically useful instruments, including:
- Family history of asthma and allergic diseases;
- Personal history of atopy or asthma; use of bronchodilator substances; other, also occasional, allergic disorders;
- Physical and complete examination (lung auscultation is often quite normal);
- Evaluation of presence or influence of environmental factors (cigarette smoke, smog, pollen, animal dander, dust mites, cold or dry air);
- Blood cell count and erythrocyte sedimentation rate (infections);
- Chest x-ray (chronic pulmonary diseases, fibrosis, lymphoadenopathy, cardiomegaly);
- Skin allergy tests (prick test), IgE and RAST (allergic problems);
- Heart clinic and instrumental evaluation (ECG and/or echocardiogram).

Diagnostic Tests

1. **Pulmonary function testing** is the next diagnostic step. Note that the pulmonary function tests should be performed on days free from asthma symptoms and concurrent problems (rhinitis, allergies, sinusitis), without any prior short-acting bronchodilator therapy in the previous eight to 12 hours, and any long-acting bronchodilator therapy in the previous 48 hours (IAAF Beta-2 Agonist Protocol). Antileukotrienes should be suspended in the 96 hours prior to the test; cromolyn compounds, sodium cromoglycate, nedocromil sodium and ipratroprium bromide in the last 12-24 hours; and antihistamines in the last 48 hours. In addition, inhaled steroids should not be administered on the day of the test; no caffeine should be taken the morning of the test; and no vigorous exercise should be performed in the four to six hours prior to the test, or preferably on the day of the test at all.

2. Laboratory **basal spirometry** is good for a simple and standard evaluation (Flow Volume Curve, FVC, FEV1, FEV1/FVC, PEFR, FEF 25-75). In athletes with solitary EIA, the basal FEV1 will be normal, over 80% of predicted normal value, while in asthmatic athletes it will be lower than 80%. For daily, practical, and on-field self-evaluation, athletes can use small and inexpensive peak flow meters.

3. **Exercise challenge tests** are commonly performed in the laboratory, using treadmill, or stationary cycle, or rowing equipment. Sometimes an exercise test performed running free and outside, as in natural conditions, is practical, but it is less controlled in its intensity[41]. However, for athletes, the chance to perform the specific field test of their sport is optimal for diagnosis. For exercise challenge tests (Figure 1):

- No warm-up is allowed to avoid a direct bronchospasm.
- The intensity and duration of aerobic exercise should be 80-95% of the maximum heart rate for 6-10 minutes, possibly without crossing the anaerobic threshold, to avoid the exhaustion of the athlete and the release of catecholamines.
- The inhaled air should have a relative humidity below 50% and an ambient temperature of 20-25°C; the use of inhaled cold air (-20°C) during the exercise test increases the sensitivity in diagnosing EIB, without decreasing specificity.
- After the exercise test, spirometric measurements are conducted every three to five minutes for 15-30 minutes, and eventually after 4-12 hours, in late responders.
- A decrease of FEV1 of 10% or more is considered positive for EIA. The severity of disease is classified as mild (10-20%), moderate (20-40%), and severe (more than 40%). Reversibility of bronchospasm after an inhaled bronchodilator will confirm the diagnosis.

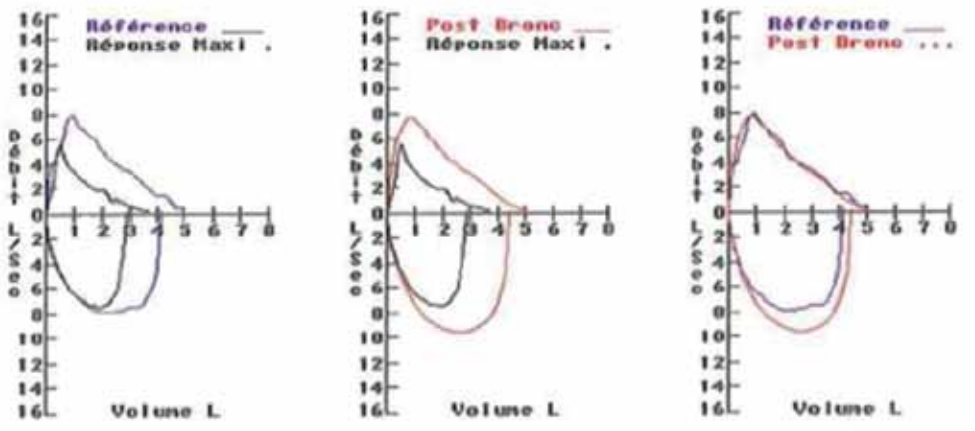

Figure 1: Example of Exercise Challenge Test (Reference (basic curve). Max. response after exercise. Complete reversibility post-bronchodilator.

4. **Pharmacological challenge tests** can be used to assess asthma, while being less specific and sensitive for EIA. The methacholine test, which is more sensitive and less specific, induces bronchoconstriction mainly in the distal bronchi, and increases airway inflation pressure and contraction of the trachealis muscle; histamine causes airway obstruction by activation of bronchial smooth muscle and mediator receptors[46]. Both for histamine and methacholine, cut-off levels are defined, in terms of concentration or cumulated dose, able to induce a 20% reduction of FEV1 (PC-20 or PD-20). Particularly for the methacholine test (the histamine test is not formally accepted for athletes), different cut-off levels are chosen on the basis of specificity rather than sensitivity for methacholine challenges to identify people with asthma, and for taking into account possible previous treatment for long periods with inhaled glucocorticosteroids.

5. **Osmotic tests** include the dry powdered mannitol inhalation challenge and the nebulised hypertonic saline challenge. Increased doses of the stimulating substance are followed by pulmonary function tests until cut-off levels. Both tests act by altering the osmolarity of airway surface liquid (ASL) with release of mediators from sensitised mastcells. The osmotic tests are sensitive and specific, easy to perform, and economical [43, 48].

6. The **eucapnic voluntary hyperventilation (EVH)** challenge can, in susceptible individuals, induce bronchoconstriction with increased ventilation rate by drying the airway surface liquid and changing the osmolarity of inflammatory cells. In athletes, the respiration rate achieved should be almost 85% of MVV (maximal ventilation rate), about 35 times FEV1. The test is performed with a dry air mixture containing 4.5% or 5% CO_2 to ensure eucapnia and protect from the hypocapnia induced by hyperventilation; this latter, in fact, may cause indistinct bronchoconstriction both in EIB positive and negative subjects. The inspired air can also be chilled, although chilling is not necessary [42, 47] (Figure 2).

7. The **bronchodilator test** is an indirect but limited method used to detect airway obstruction by airways reversibility to inhaled short-acting bronchodilators (terbutaline or salbutamol), when the resting FEV1 is below 70% of normal (it should not be ethical, in fact, to perform other different tests while starting from a basic bronchoconstriction). The response is variable, and the cut-off criteria for a positive test is 12% FEV1 increase compared with baseline (and in any case not less than 200 ml), as recently stated by the European Respiratory Society[45].

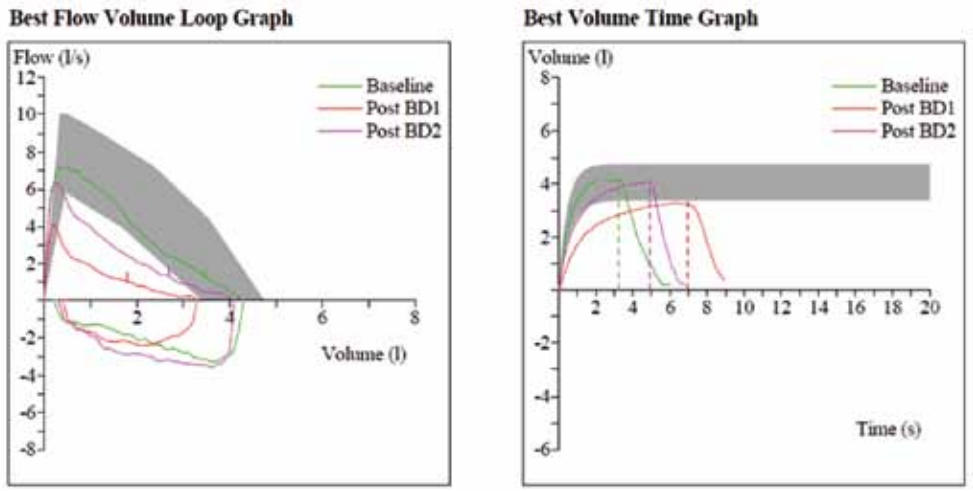

Figure 2: Example of Eucapnic Voluntary Hyperventilation Test (Baseline, BD1(Post EVH) and BD2 (reversibility post bronchodilator).

Further tests by inhalation of adenosine monophosphate (AMP) or carbachol or acethylcoline, or by other indirect stimuli have also been used to assess bronchial responsiveness, including inhalation of simple dry air, or better, cold and dry air, even if less commonly.

Note that a combination of tests, as exercise test with cold air inhalation, might increase, in some conditions, the sensitivity, without loosing specificity.

Treatment of Asthma and EIB

The treatment of athletes with asthma or EIA or EIB, compared to normal population, requires more attention not only on the general prevention of disease symptoms, but also on necessities of sport performance, considering the different levels of exercise stress [50, 51].

Non-Pharmacologic Treatment

Even when starting with specific therapeutic drugs, a non-pharmacologic treatment should be first adopted, based on the following criteria.

1. Education of athletes, coaches, and families is a primary component: the disorder is frequent and common in the population, and does not limit performance when adequately treated.

2. Prevention is the main method: avoiding cold or dry air, by training indoors, or covering the mouth and nose with a scarf during winter, or using a mask to warm and humidify the air may be helpful.

3. Predominant nasal, more than mouth breathing, may reduce EIB by inhaling more warmed and humidified air.

4. Exercise conditioning to lower ventilation rate decreases airway responsiveness.

5. Warming up well before exercise, with repeated short and high intensity exercises, may induce, as above mentioned, after a possible reversible bronchoconstriction phase lasting less than 1 hour, a refractory period useful during competition and may partially reduce the need for pre-medication.

6. Avoid training sessions that risk possible exposure to environmental situations of airborne allergens or irritants.

7. Avoid consumption of foods with possible allergens, at least in the last four hours before an exercise or competition session.

8. Reduce training when exacerbation periods of rhinitis, sinusitis, or allergy are present.

9. Stop training during viral respiratory infections or acute bronchial exacerbations.

Pharmacologic Treatment

The treatment of seasonal allergic rhinitis by non-sedating anti-histamines or local intranasal glucocorticosteroids is an important step in preventing bronchial hyper-reactivity[52]. Generally, the correct use of medications, when needed, will help the patients to train well and live better, without pharmaceutical addiction and with limited adverse effects, both of which are possible risks of inhaled beta-2 agonists. Proper inhalation of the medication will result in a better deposition of the substances into the bronchial system: after slow expiration, controlled breathe while inhaling to total lung volume and holding the breath for 10 seconds will enhance deposition. A pause of 30 second between the two inhalations will increase the quantity of drug delivered into the lungs. While describing beta-2 agonists, we will mention those most commonly used by athletes.

1. **Short-acting beta-2 agonists** (salbutamol/albuterol, terbutaline) administered by inhalation 20-30 minutes before exercise have a peak bronchodilator effect within 60 minutes, and maximal duration of tree to four hours. Used at a dosage of 200-400mcg for salbutamol or 500-1000mcg for terbutaline, they are effective in 90% of EIB, lasting up to 3-4 hrs[54].

2. **Long-acting beta-2 agonists** (formoterol and salmeterol) need to be administered well in advance before exercise; even if some studies were able to show a start of effect within 30 minutes, they have their maximal effect in four hours and may last up to 8-12 hours, permitting the prevention of EIB and asthma attacks in prolonged exercise sessions and in the

night. They should be used together with inhaled glucocorticosteroids and this combination is suggested and seems to work better both for acute exacerbations and for long term treatment[56]. The beta-2 agonists, both short- and long-acting, work by increasing intracellular concentration of cyclic adenosine monophosphate (cAMP), which modulates the relaxation of bronchial smooth muscle and inhibits the release of mediators from mast cells. Even if being beta-2 selective, they interact (short-acting more than long acting ones) with alpha and beta-1 receptors, causing tachycardia, tremors, and palpitations. These secondary cardiovascular effects should keep the athletes aware of the risks connected with long-term and uncontrolled abuse of beta-2 agonists. Sometimes they induce tachyphylaxis, worsening asthma[57]. By continuous use, the beta-2 agonists (the long-acting more than the short-acting) become ineffective in two to three years for induced tolerance, and of course reduced protective effect also on EIA or EIB. At lower level, the tolerance starts also after two to three months of continuous use, and is not surely prevented by the association with GCSs. For these reasons, it should be better, from time to time, to discontinue their use[58, 59].

3. **Inhaled glucocorticosteroids (GCS)** (beclomethasone dipropionate, budesonide, ciclesonide, fluticasone propionate, flunisolide, momethasone, triamcinolone acetonide, etc.) are practically long-term drugs. They are not effective on an as-needed basis, but are useful for chronic asthma; in EIA, even if some antinflammatory action might start in one to two weeks, the main effects will start when used for at least one month, particularly if used in association when the beta-2 agonists are not effective when used individually. They suppress the production of cytokines, reducing the eosinophils, and preventing inflammatory mediators release [60, 61, 62]. Adverse effects are dysphonia, oral irritation, cough and candidiasis. Some systemic effects due to high dosage for long periods, might induce adrenal suppression and decreased bone mineral density, normally uncommon in athletes.

4. **Leukotriene antagonists** are used for long-term asthma therapy. Montelukast, Pranlukast and Zafirlukast are leukotriene antagonists, while Zileuton is an inhibitor of biosynthesis by 5-lipoxygenase; they are effective in preventing EIA in chronic asthma. Leukotrienes are products of arachidonic acid metabolism, and increase eosinophil migration, mucus production, and bronchial oedema, with bronchoconstriction response 1000 times greater than histamine. The antileukotrienes, normally used orally for long-term therapy, offer 24-hour protection with very low adverse effects (dyspepsia, nausea). Even if sometimes they are used alone, they work better when associated with inhaled GCSs and/or long acting beta-2 agonists, mainly in the prevention of EIB, even if not in all athletes[64].

5. **Cromolyn compounds** (Cromolyn sodium and Nedocromil sodium) are mastcell stabilisers without bronchodilator effects, and are useful, when inhaled 20 minutes before exercise, in preventing EIB and EIA symptoms in 80% of patients, by inhibiting the prostaglandins increase in response to an osmotic stimulus. They may also prevent the late-phase response of EIA. They can be used many times a day in the absence of adverse effects, and may be additive when beta-2 agonists are not completely effective. Adverse effects include bad taste, throat irritation, cough, nausea, vomiting, and abdominal pain[63, 65, 67].

6. **Inhaled anticholinergics** (ipratropium bromide, oxitropium bromide, tiotropium bromide) do not have unanimous consensus on their efficiency in preventing EIA, and are tendentially used in chronic obstructive pulmonary diseases and chronic bronchial infections complicated by asthmatic attacks[66].

7. **Antihistamines** (astemizole, cetirizine, chlorpheniramine, desloratidine, phexophenadine, terphenadine, etc.) exhibit little effect; they might be useful in allergic asthma only when the disease is combined with allergic rhinitis due to air pollens[68]. The oral dryness and some mild sedative effects are not helpful for athletes. Further, they are sometimes combined with stimulants not permitted by anti-doping rules. Ketotiphen is a more widely used antihistamine substance; like cromolyn compounds, it acts on mast cells as a stabiliser, with fewer adverse effects.

8. **Antibiotics** are used in the presence of infections - sinusitis, rhinitis, bronchitis - that increase bronchial sensitivity.

9. **Methylxanthines** (theophylline and aminophylline or theophylline ethylendiamine) work by decreasing the metabolism of cAMP by inhibition of phosphodiesterase; they also have adrenergic effects. They are used systemically (oral or injections), mainly in chronic asthma and in acute exacerbations, under strict medical control for possible adverse effects (tachyarrhythmias, hypertension, peptic ulcers, hyperthyroidism, seizure disorders). Sustained-release theophylline formulations for once- or twice-daily dosing are in use, but with relative efficiency as long-term control[69].

10. **Systemic glucocorticosteroids and beta-2 agonists** are restricted to more serious conditions and are administered in emergency situations by medical prescription. Of course, the collateral effect of both drug categories are more frequent, according to the duration of therapy.

11. **Anti-IgE** (omalizumab) is used in patients with elevated serum levels of IgE, normally as additional therapy to GCSs and beta-2 agonists. The high cost/efficiency, at the moment, is a limit to a larger use[70].

12. **Epinephrine** (adrenaline) is administered subcutaneously, under strict medical control, only in life-threatening emergency situations.

Doping Related Issues

Since 1993, the beta-2 agonists have been subject to restrictions by the IOC and IAAF, based on their possible effects as anabolic agents[55, 80]. However, a large increase in the number of athletes which declared use of inhaled beta-2 agonists was reported in high-level competitions and Olympic Games, perhaps as a consequence of an incomplete or erroneous diagnosis and, sometimes due to an over-use or acquired tolerance to beta-2 agonists, with an under-use of inhaled glucocorticosteroids[79].

In the past and recent years, many scientific papers were published on the effects in animals and humans of systemic use (oral or infusion) of different beta-2 agonists, which can potentially have positive ergogenic effects on skeletal muscle anabolism, and on aerobic and anaerobic performance[72, 74, 75]. For this reason, and based also on the demonstrated use by cheating athletes since the early 1990s, clenbuterol was included, some years ago, in the list of anabolic agents[71].

On the other side, varying results are reported in scientific papers on the possible ergogenic effects of inhaled beta-2 agonists, both short-acting (salbutamol, terbutalin, fenoterol) or long-acting (salmeterol and formoterol), in normal or in asthmatic athletes[73, 76, 77, 78].

As a consequence of this, the use of beta-2 agonists, in the last 15 years, has been subjected to progressively stricter rules[81]. According to the 2009 WADA prohibited list, in force until 31.12.2009, all beta-2 agonists including their D- and L-isomers were prohibited. Therefore, formoterol, salbutamol, salmeterol and terbutaline when administered by inhalation required a Therapeutic Use Exemption, and, despite the granting of a Therapeutic Use Exemption, and the presence of salbutamol in urine in excess of 1000 ng/mL was considered as an Adverse Analytical Finding[82].

With the 2010 version of WADA list, in force since 01.01.2010, the formal situation changed a little bit, and, while clenbuterol remained banned inside other anabolic agents, for all the other beta-2 agonists, included in the substances and methods banned at all times, “both In and Out of competition”, it is stated that:

“All beta-2 agonists (including both optical isomers where relevant) are prohibited except salbutamol (maximum 1600 micrograms over 24 hours) and salmeterol by inhalation which require a declaration of Use in accordance with the International Standard for Therapeutic Use Exemptions. The presence of salbutamol in urine in excess of 1000 ng/mL is presumed not to be an intended therapeutic use of the substance and will be considered as an Adverse Analytical Finding unless the Athlete proves, through a controlled pharmacokinetic study, that the abnormal

result was the consequence of the use of a therapeutic dose (maximum 1600 micrograms over 24 hours) of inhaled salbutamol".

In the 2011 WADA list, while maintaining the same position, a small change in the definition erased the necessity of declaration of use, limiting only the salbutamol and salmeterol use as: "when taken by inhalation, in accordance with the manufacturers' recommended therapeutic regime".

According to the 2010 WADA list GCSs are banned only "In competition":

"All glucocorticosteroids are prohibited when administered by oral, intravenous, intramuscular or rectal routes. In accordance with the International Standard for Therapeutic Use Exemptions, a declaration of Use must be completed by the Athlete for glucocorticosteroids administered by intraarticular, periarticular, peritendinous, epidural, intradermal and inhalation routes, except as noted below. Topical preparations when used for auricular, buccal, dermatological (including iontophoresis/phonophoresis), gingival, nasal, ophthalmic and perianal disorders are not prohibited and require neither a Therapeutic Use Exemption nor a Declaration of Use".

Also for glucocorticosteroid use, the 2011 WADA list changed, defining only that:

"All glucocorticosteroids are prohibited when administered by oral, intravenous, intramuscular or rectal routes", and eliminating any reference to declaration of use.

About the "declaration of use", in the 2010 version of the WADA International standard on TUE it is specified that:

"The Prohibited List identifies certain substances and methods that are not prohibited but for which an Athlete is required to file a declaration of Use. An Athlete should satisfy this requirement by declaring the Use on a Doping Control Form and when available by filing a declaration of Use through ADAMS".

Of course, independent of the new updated statements, a declaration on the doping control form (or in ADAMS if any) is advisable for the above mentioned substances.

Since 2003, the IAAF introduced a beta-2 agonists protocol, periodically updated, on the same position of IOC for the Olympic Games, regarding applications and approvals of therapeutic use exemptions for inhaled beta-2 agonists (available on IAAF website). Based on this protocol, athletes are required to submit, together with the TUE application, the following:

- "detailed medical record" with precise diagnosis and relevant medical information concerning the individual condition;
- "objective evidence of asthma and/or exercise-induced asthma (EIA) or EIB through the provision of test results (provocation tests) and supporting documentation";
- details of medical or hospital consultations;
- details of medication prescribed in the last 6 months, and particularly of medications in the last three months before provocation test.

Concerning the provocation tests, only the following are accepted by IAAF, and only if the conditions mentioned are met:

1. **Bronchodilator Test:** after administering a "permitted" beta2 agonist by inhalation, a bronchial reversibility test is considered positive if the increase in FEV1 is 12% or more of the baseline FEV1 or the predicted FEV1 and exceeds 200ml.

2. **Eucapnic Voluntary Hyperpnea Test:** considered positive when a fall in FEV1 of 10% or more from baseline is recorded after a 6 minutes period of hyperpnea in dry air.

3. **Exercise challenge in the laboratory or an exercise test in the field:** positive when there is a fall in FEV1 of 10% or more compared to baseline during the first 30 minutes post exercise.

4. **Hyperosmolar Aerosols:** a fall in FEV1 of 15% or more from baseline after inhaling 22.5ml of 4.5gm% saline (e.g. 4.5g NaCl/100ml water) or a dose of 635mg of dry powdered mannitol is a positive response and is consistent with a diagnosis of currently active asthma or EIA/EIB. The response to 4.5% saline and the response to mannitol is usually reported as the dose re-

quired to provoke a 15% fall in FEV1 (PD15) but should also be reported as the maximum fall after the final dose of aerosol.

5. **Methacholine Test:** a test is considered positive if there is a fall in FEV1 of 20% or more from baseline at a dose (PD20) less than or equal to 400 microgram / 2 micromoles (cumulative dose) or 200 micrograms /1 micromole (non cumulative dose) or a concentration (PC20) less than or equal to 4 mg/ml (tidal breathing technique American Thoracic Society guidelines 1999) when the subject is not taking inhaled corticosteroids or has taken them for less than one month. For applicants taking inhaled corticosteroids for at least one month, the PD20 should be less than or equal to 1600 micrograms/8.0 micromoles (cumulative dose) or 800 micrograms/4.0 micromoles (non cumulative dose), or a PC20 less than or equal to 16.0 mg/ml (tidal breathing ATS guidelines 1999) to be accepted as proof of airway hyperresponsiveness (AHR).

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. Graphic evidence of the tests (ie. flow volume curves) should be enclosed with the TUE application, otherwise they will be requested (see Figure 3).

Conclusion

Some suggestions for the athletes with asthma and/or EIB or EIA:

1. A sure diagnosis and not a self-diagnosis is needed before starting with therapy.

2. Prevention should be the first therapeutic approach to this pathology.

3. The abuse or frequent use or long term use of beta-2 agonists is able to produce tolerance, and less effectiveness in asthma or EIB prevention.

4. Long-term therapy with inhaled GCSs is encouraged.

5. Long-acting inhaled beta-2 agonists should be normally used together with inhaled GCSs, and never alone.

6. A continuous check of the yearly up-dated WADA list of banned substances and methods and of IAAF rules and regulations, is needed to verify possible changes of the lists and consequently of the rules and the protocols.

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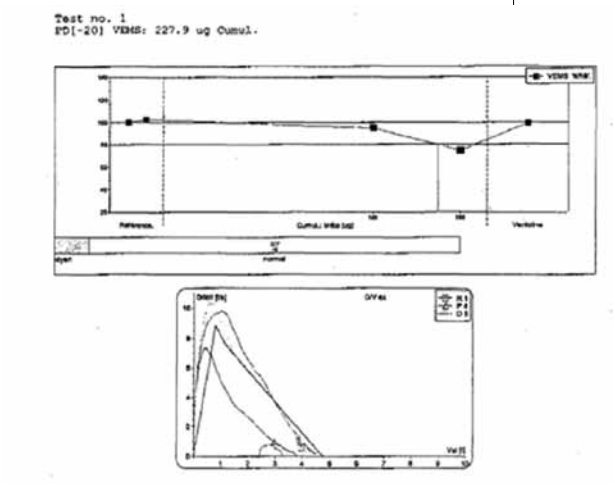

Figure 3: Example of methacholine provocation test with PD20 FEV1 227,9 mcg

REFERENCES

1 MCFADDEN, E. R.; GILBERT, I. A. (1994). Exercise-induced asthma. N Engl J Med, 330, 1362-1367.

2 HOUGH, D. O.; DEC, K. L. (1994). Exercise-induced asthma and anaphylaxis. Sports Med, 18, 162-172.

3 TAN, R. A.; SPECTORM S. L. (1998). Exercise-induced asthma. Sports Med, 25,1-6.

4 BECK, K. C. (1999) Control of airway function during and after exercise in asthmatics. Med Sci Sports Exerc, 31, s4-s11.

5 LANGDEAU, J. B.; BOULET, L. P. (2001). Prevalence and mechanisms of development of asthma and airway hyperresponsiveness in athletes. Sports Med, 31, 601-616

6 STORMS, W. W. (1999). Exercise-induced asthma: diagnosis and treatment for the recreational or elite athlete. Med Sci Sports Exerc, 31, s33-s38.

7 RUNDELL, K. W.; JENKINSON, D. M. (2002). Exercise-induced bronchospasm in elite athletes. Sports Med, 32, 583-600.

8 LANGDEAU, J.B.; TURCOTTE, H.; BOWIE, D.M.; JOBIN, J.; DESGAGNE, P.; BOULET, L.P. (2000). Airway hyperresponsiveness in elite athletes. Am J Respir Crit Care Med, 2000, 161, 1479-1484

9 HELENIUS, I.; HAAHTEL, T. (2000). Allergy and asthma in elite summer sports athletes. J Allergy Clin Immunol, 106, 444-452.

10 ANDERSON, S.D.; SUE-CHU, M.; PERRY, C.P.; GRATZIOU, C.; KIPPELEN, P.; MCKENZIE, D.C. et al. (2006). Bronchial challenges in athletes applying to inhale a beta2-agonist at the 2004 Summer Olympics. J Allergy Clin Immunol, 2006, 117, 767–773.

11 WILBER, R.L.; RUNDELL, K.W.; SZMEDRA, L.; JENKINSON, D.M.; IM, J.; DRAKE, S.D. (2000). Incidence of exercise-induced bronchospasm in Olympic winter sport athletes. Med Sci Sports Exerc, 32, 732-737.

12 MAIOLO, C.; FUSO, L.; TODARO, A.; ANATRA, F.; BONIELLO, V.; BASSO, S. et al. (2004). Prevalence of asthma and atopy in Italian Olympic athletes. Int J Sports Med, 25, 139-144.

13 DICKINSON, J.W.; WHYTE, G.P.; MCCONNELL, A.K.; HARRIES, M.G. (2005). Impact of changes in the IOC-MC asthma criteria: a British perspective. Thorax, 60, 629-632.

14 FITCH, K.D. (2006). Beta2-agonists at the Olympic Games. Clin Rev Allergy Immunol, 31, 259-268.

15 ANDERSON, S.D.; FITCH, K.; PERRY, C.P.; SUE-CHU, M.; CRAPO, R.; MCKENZIE, D. et al. (2003). Responses to bronchial challenge submitted for approval to use inhaled beta2-agonists before an event at the 2002 Winter Olympics. J Allergy Clin Immunol 111, 45-50.

16 BOUSQUET, J.; VAN CAUWENBERGE, P.; KHALTAEV, N. (2001). Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol, 108(5 Suppl), S147- S334.

17 RUNDELL, K.W.; SPIERING, B.A. (2003). Inspiratory stridor in elite athletes. Chest, 123, 468-474.

18 MICKLEBOROUGH, T.D.; GOTSHALL, R.W. (2003). Dietary components with demonstrated effectiveness in decreasing the severity of exercise-induced asthma. Sports Med, 33, 671-81.

19 ADIR, Y.; SHUPAK, A.; GIL, A.; PELED, N.; KEYNAN, Y.; DOMACHEVSKY, L. et al. (2004). Swimming-induced pulmonary edema: clinical presentation and serial lung function. Chest, 126, 394-399.

20 ANDERSON, S. D.; HOLZER, K. (2000). Exercise-induced asthma: is it the right diagnosis in elite athletes? J Allergy Clin Immunol, 106, 419-428.

21 SHADICK, N.A.; LIANG, M.H.; PARTRIDGE, A.J.; BINGHAM, C.; WRIGHT, E.; FOSSEL, A.H. et al. (1999). The natural history of exercise-induced anaphylaxis: survey results from a 10- year follow-up study. J Allergy Clin Immunol, 104, 123-127.

22 BUSSE, W.W.; LEMANSKE, R.F. (2001). Asthma, N Engl J Med, 344(5), 350-62.

23 ANDERSON, S.D.; DAVISKAS, E. (2000). The mechanism of exercise-induced asthma is…. J Allergy Clin Immunol, 106, 453-459.

24 HALLSTRAND, T.S.; MOODY, M.W.; WURFEL, M.M.; SCHWARTZ, L.B.; HENDERSON, W.R.; AITKEN, M.L. (2005). Inflammatory basis of exercise-induced bronchoconstriction. Am J Respir Crit Care Med, 172, 679-686.

25 BOULET, L.P.; TURCOTTE, H.; LANGDEAU, J.B.; BERNIER, M.C. (2005). Lower airway inflammatory responses to high-intensity training in athletes. Clin Invest Med, 28, 15-22.

26 HALLSTRAND, T.S.; MOODY, M.W.; AITKEN, M.L.; HENDERSON, W.R. (2005). Airway immunopathology of asthma with exercise-induced bronchoconstriction. J Allergy Clin Immunol, 116, 586-593.

27 O'SULLIVAN, S.; ROOQUET, A.; DAHLE, N.B.; LARSEN, F.; EKLUND, A.; KUMLIN, M. et al. (1998). Evidence for mast cell activation during exercise-induced bronchoconstriction. Eur Respir J, 12, 345-350.

28 HELENIUS, I.J.; TIKKANEN, H.O.; HAAHTELA, T. (1997). Association between type of training and risk of asthma in elite athletes. Thorax, 52, 157-160.

29 BJERMER, L.; ANDERSON, S.D. (2005). Bronchial hyperresponsiveness in athletes: mechanisms for development. In: Carlsen, K.H.; Delgado, L.; Del Giacco, S. edtors.

Diagnosis, prevention and treatment of exercise-related asthma, respiratory and allergic disorders in sports. Sheffield, UK: European Respiratory Society Journals Ltd, 19-34.

30 BONSIGNORE, M.R.; MORICI, G.; RICCOBONO, L.; PROFITA, M.; BONANNO, A.; PATERNO, A. et al. (2003). Airway cells after swimming outdoors or in the sea in non-asthmatic athletes. Med Sci Sports Exerc, 35, 1146-1152.

31 HOLGATE ST.: Genetic and environmental interaction in allergy and asthma. J Allergy Clin Immunol 1999, 104(6), 1139-46.

32 DROBNIC, F.; HAAHTELA, T. (2005). The role of the environment and climate in relation to outdoor and indoor sports. In: Carlsen, K.H.; Delgado, L.; Del Giacco, S. editors. Diagnosis, prevention and treatment of exercise-related asthma, respiratory and allergic disorders in sports. Sheffield, UK: European Respiratory Society Journals Ltd, 35-47.

33 VARRASO, R.; MASSIN, N.; HERY, M.; FRADIER-DUSCH, M.; MICHAELY, J.P.; FOURNIER, M. et al. (2002). Not only training but also exposure to chlorinated compounds generates a response to oxidative stimuli in swimmers. Toxicol Ind Health, 18, 269-278.

34 RUNDELL, K.W. (2003). High levels of airborne ultrafine and fine particulate matter in indoor ice arenas. Inhal Toxicol, 15, 237-250.

35 OMORI, C.; SCHOFIELD, B.H.; MITZNER, W.; FREED, A.N. (1995). Hyperpnea with dry air causes time-dependent alterations in mucosal morphology and bronchovascular permeability. J Appl Physiol, 78, 1043-1051.

36 GILBERT, I.A.; MCFADDEN, E.R. Jr (1992). Airway cooling and rewarming. The second reaction sequence in exercise-induced asthma. J Clin Invest, 90, 699-704.

37 RUNDELL, K. W.; IM, J.; MAYERS, L. B.; WILBER, R. L.; SZMEDRA, L.; SCHMITZ, H. R. (2001). Self-reported symptoms and exercise-induced asthma in the elite athlete. Med Sci Sports Exerc, 33, 208-213.

38 TURCOTTE, H.; LANGDEAU, J.B.; BOWIE, D,M.; BOULET, L.P. (2003). Are questionnaires on respiratory symptoms reliable predictors of airway hyperresponsiveness in athletes and sedentary subjects? J Asthma, 40, 71-80.

39 MCFADDEN, E.R.JR; ZAWADSKI, D.K. (1996). Vocal cord dysfunction masquerading as exercise-induced asthma. A physiologic cause for ''choking'' during athletic activities. Am J Respir Crit Care Med, 153, 942-947.

40 CARLSEN, K.H.; ENGH, G.; MORK, M. (2000). Exercise induced bronchoconstriction depends on exercise load. Respir Med, 94, 750-755.

41 RUNDELL, K.W.; WILBER, R.L.; SZMEDRA, L.; JENKINSON, D.M.; MAYERS, L.B.; IM, J. (2000). Exercise-induced asthma screening of elite athletes: field versus laboratory exercise challenge. Med Sci Sports Exerc, 32, 309-316.

42 RUNDELL, K.W.; ANDERSON, S.D.; SPIERING, B.A.; JUDELSON, D.A. (2004). Field exercise vs laboratory eucapnic voluntary hyperventilation to identify airway hyperresponsiveness in elite cold weather athletes. Chest, 125, 909-915.

43 DICKINSON, J.W.; WHYTE, G.P.; MCCONNELL, A.K.; HARRIES, M.G.: (2006). Screening elite winter athletes for exercise induced asthma: a comparison of three challenge methods. Br J Sports Med, 40, 179-182.

44 HELENIUS, I.; TIKKANEN, H.O.; HAAHTELA, T. (1998). Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. Br J Sports Med, 32, 125-129.

45 CARLSEN, K.H.; ANDERSON, S.D.; BJERMER, L.; BONINI, S.; BRUSASCO, V.; CANONICA, W.; CUMMINSKEY, J.; DELGADO, L.; DEL GIACCO, S.; DROBNIC, F.; HAAHTELA, T.; LARSSON, K.; PALANGE, P.; POPOV, T.; VAN CAWENBERGE, P.: (2008). Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: Part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. Allergy, 63, 387-403.

46 COCKCROFT, D.W.; DAVIS, B.E.; TODD, D.C.; SMYCNIUK, A.J. (2005). Methacholine challenge: comparison of two methods. Chest, 127, 839-844.

47 ANDERSON, S.D.; ARGYROS, G.J.; MAGNUSSEN, H.; HOLZER, K. (2001). Provocation by eucapnic voluntary hyperpnoea to identify exercise induced bronchoconstriction. Br J Sports Med, 35, 344-347.

48 HOLZER, K.; ANDERSON, S.D.; CHAN, H.K.; DOUGLASS, J. (2003). Mannitol as a challenge test to identify exercise-induced bronchoconstriction in elite athletes. Am J Respir Crit Care Med, 167, 534-537.

49 GINA Global initiative for asthma – Global strategy for asthma management and prevention revised 2006 MCR VISION, Inc., www.ginasthma.org.

50 CARLSEN, K.H.; ANDERSON, S.D.; BJERMER, L.; BONINI, S.; BRUSASCO, V.; CANONICA, W.; CUMMINSKEY, J.; DELGADO, L.; DEL GIACCO, S.R.; DROBNIC, F.; HAAHTELA, T.; LARSSON, K.; PALANGE, P.; POPOV, T.; VAN CAWENBERGE, P. (2008). Treatment of exercise-induced asthma, respiratory and allergic disorders in sports and the relationship to doping: Part II of the report from the Joint Task Force of European Respiratory Society(ERS) and European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. Allergy, 63, 492-505.

51 LARSSON, K.; CARLSEN, K.H.; BONINI, S. (2005). Antiasthmatic drugs: treatment of athletes and exercise-induced bronchoconstriction. In: Carlsen, K.H.; Delgado, L.; Del Giacco, S. editors. Diagnosis, prevention and treatment of exercise-related asthma, respiratory and allergic disorders in sports. Sheffield, UK: European Respiratory Journals Ltd, 73-88.

52 HELENIUS, I.; LUMME, A.; HAAHTELA, T. (2005). Asthma, airway inflammation and treatment in elite athletes. Sports Med, 35, 565-574.

53 GINA Pocket Guide for Physicians and Nurses based on Global strategy for asthma management and prevention - 2006 Medical Communications Resources, Inc. www.ginasthma.org.

54 ANDERSON, S.D.; CAILLAUD, C.; BRANNAN, J.D. (2006). Beta2-agonists and exercise-induced asthma. Clin Rev Allergy Immunol 31, 163-180.

55 CARLSEN, K.H.; INGJER, F.; THYNESS, B.; KIRKEGAARD, H. (1997). The effect of inhaled salbutamol and salmeterol on lung function and endurance performance in healthy well-trained athletes. Scand J Med Sci Sports, 7, 160-165.

56 NELSON, J.; STRAUSS, L.; SKOWRONSKI, M.; CIUFO, R.; NOVAK R.; MCFADDEN, E.R. Jr (1998). Effect of long-term salmeterol treatment on exercise-induced asthma. N Engl J Med, 339, 141-146.

57 SALPETER, S.R. (2004). Cardiovascular safety of beta-2-adrenoceptor agonist use in patients with obstructive airway disease: a systematic review. Drugs Aging, 21, 405-414.

58 DAVIS, B.E.; REID, J.K.: COCKCROFT, D.W. (2003). Formoterol thrice weekly does not result in the development of tolerance to bronchoprotection. Can Respir J, 10, 23-26.

59 SALPETER, S.R.; ORMISTON, T.M.; SALPETER, E.E. (2004). Meta-analysis: respiratory tolerance to regular beta2-agonist use in patients with asthma. Ann Intern Med, 140, 802-813.

60 JONASSON, G.; CARLSEN, K.H.; HULTQUIST, C. (2000). Low-dose budesonide improves exercise- induced bronchospasm in school children. Pediatr Allergy Immunol, 11, 120-125.

61 KOSKELA, H.O.; HYVARINEN, L.; BRANNAN, J.D.; CHAN, H.K.; ANDERSON, S.D. (2000). Sensitivity and validity of three bronchial provocation tests to demonstrate the effect of inhaled corticosteroids in asthma. Chest, 124, 1341-1349.

62 SUBBARAO, P.; DUONG, M.; ADELROTH, E.; OTIS, J.; OBMINSKI, G.; INMAN, M. et al. (2006). Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma. J Allergy Clin Immunol, 117, 1008-1013.

63 ANDERSON, S.D.; RODWELL, L.T.; DAVISKAS, E.; SPRING, J.F.; DU TOIT J. (1996). The protective effect of nedocromil sodium and other drugs on airway narrowing provoked by hyperosmolar stimuli: a role for the airway epithelium? J Allergy Clin Immunol, 2, S124-134.

64 RUNDELL, K.W.; SPIERING, B.A.; BAUMANN, J.M.: EVANS TM. (2005). Effects of montelukast on airway narrowing from eucapnic voluntary hyperventilation and cold air exercise. Br J Sports Med, 39, 232-236.

65 BRANNAN, J.D.; GULLIKSSON, M.; ANDERSON, S.D.; CHEW, N.; SEALE, J.P.; KUMLIN, M. (2006). Inhibition of mast cell PGD2 release protects against mannitol-induced airway narrowing. Eur Respir J, 27, 944-950.

66 FREEMAN, W.; JAVAID, A.; CAYTON, R.M. (1992). The effect of ipratropium bromide on maximal exercise capacity in asthmatic and non-asthmatic men. Respir Med, 86, 151-155.

67 SPOONER, C.H.; SAUNDERS, L.D.; ROWE, B.H. (2000). Nedocromil sodium for preventing exercise-induced bronchoconstriction. Cochrane Database Syst Rev, 2, CD001183.

68 SLATER, J.W.; ZECHNICH, A.D.; HAXBY, D.G. (1999). Second-generation antihistamines: a comparative review. Drugs, 57(1), 31-47.

69 BARNES, P.J. (2003). Theophylline: new perspectives for an old drug. Am J Respir Crit Care Med, 167(6), 813-8.

70 HOLGATE, S.T.; CHUCHALIN, A.G.; HEBERT, J.; LOTVALL, J.; PERSSON, G.B.; CHUNG, K.F. et al. (2004). Efficacy and safety of a recombinant antiimmunoglobulin E antibody (omalizumab) in severe allergic asthma. Clin Exp Allergy, 34(4), 632-8.

71 DODD, S.L.; POWERS, S.K.; VRABAS, I.S.; CRISWELL, D.; STETSON, S.; HUSSAIN, R. (1996). Effects of clenbuterol on contractile and biochemical properties of skeletal muscle. Med Sci Sports Exerc, 28, 669-676.

72 VAN BAAK, M.A.; MAYER, L.H.; KEMPINSKI, R.E.; HARTGENS, F. (2000). Effect of salbutamol on muscle strength and endurance performance in nonasthmatic men. Med Sci Sports Exerc 32, 1300-1306.

73 CARLSEN, K.H.; HEM, E.; STENSRUD, T.; HELD, T.; HERLAND, K.; MOWINCKEL, P. (2000). Formoterol turbuhaler does not improve endurance performance in healthy well trained athletes. Am J Respir Crit Care Med, 159 (3 pt 2) A412.

74 COLLOMP, K.; CANDAU, R.; MILLET, G.; MUCCI, P.; BORRANI, F.; PREFAUT, C. et al. (2002). Effects of salbutamol and caffeine ingestion on exercise metabolism and performance. Int J Sports Med, 23, 549-554.

75 VAN BAAK, M.A.; DE HON, O.M.; HARTGENS, F.; KUIPERS, H. (2004). Inhaled salbutamol and endurance cycling performance in nonasthmatic athletes. Int J Sports Med, 25, 533-538.

76 RIISER, A.; TJORHOM, A.; CARLSEN, K.H. (2006). The effect of formoterol inhalation on endurance performance in hypobaric conditions. Med Sci Sports Exerc, 38, 2132-2137.

77 MORTON, A.R.; JOYCE, K.; PAPALIA, S.M.; CARROLL, N.G.; FITCH, K.D. (1996). Is salmeterol ergogenic? Clin J Sport Med, 6, 220-225.

78 STEWART, I.B.; LABRECHE, J.M.; MCKENZIE, D.C. (2002). Acute formoterol administration has no ergogenic effect in nonasthmatic athletes. Med Sci Sports Exerc, 34, 213-217.

79 GOUBAULT, C.; PERAULT, M.C.;, LELEU, E.; BOUQUET, S.; LEGROS, P.; VANDEL, B. et al. (2001). Effects of inhaled salbutamol in exercising non-asthmatic athletes. Thorax, 56, 675-679.

80 CARLSEN, K.H.; HEM, E.; STENSRUD, T.; HELD, T.; HERLAND, K.; MOWINCKEL, P. (2001). Can asthma treatment in sports be doping? The effect of the rapid onset, long-acting inhaled b2-agonist formoterol upon endurance performance in healthy well trained athletes. Respir Med, 95, 571-576.

81 BONINI, S.; BRUSASCO, V.; CARLSEN, K. H.; DELGADO L.; GIACCO, S. D.; HAAHTELA, T.; RASI, G.; VAN CAUWENBERGE, P. B. (2004). Diagnosis of asthma and permitted use of inhaled beta-2 agonists in athletes. Allergy, 59, 33-36.

82 WEILER, J. M. (2003). Why must Olympic athletes prove that they have asthma to be permitted to take inhaled beta-2 agonists? J. Allergy Clin Immunol, 111, 36-37.