

Asthma and exercise-induced respiratory disorders in athletes. The position paper of the Polish Society of Allergology and Polish Society of Sports Medicine

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Abstract

Exercise-induced respiratory symptoms describe acute airway narrowing that occurs as a result of exercise. It includes exercise-induced bronchoconstriction (EIB) and exercise-induced asthma (EIA) issues. To provide clinicians with practical guidelines, a multidisciplinary panel of stakeholders was convened to review the pathogenesis of EIB/EIA and to develop evidence-based guidelines for the diagnosis and treatment. Recommendations for the diagnosis and treatment of EIB were developed. High-intensity exercise in polluted environment (cold air, humidity, contamination, allergens) may increase the risk of EIB and asthma symptoms in athletes. Diagnostic procedures should include history taking, physical examination, atopy assessment and functional tests of the respiratory system. A strong recommendation was made for regular use of inhaled glucocorticosteroids and avoidance of short-acting β_2 -agonists as the only treatment. The treatment of asthma in athletes should always take into account current anti-doping regulations. This position paper reflects the currently available evidence.

Key words: exercise-induced bronchoconstriction, diagnosis, treatment.

Epidemiology of exercise-induced asthma/exercise-induced bronchoconstriction

Exercise-induced respiratory symptoms are most frequently referred to as:

- exercise-induced bronchoconstriction (EIB) or
- exercise-induced asthma (EIA).

Both terms were often used interchangeably in the past. Currently it is recommended to describe exercise-induced symptoms in people without coexisting asthma and allergies as exercise-induced bronchoconstriction whereas exercise-induced asthma should be referred to as post-exercise bronchoconstriction in asthma sufferers.

Bronchoconstriction is a form of bronchial hyperreactivity which is defined as increased readiness of the bronchi to constrict in response to a variety of external factors. Bronchial hyperreactivity is the basic feature of bronchial asthma and it occurs more often in athletes than in general population, especially in swimmers and winter sports athletes [1, 2].

There is an extensive literature on the prevalence of asthma or EIB symptoms in competitive athletes. Exercise-induced asthma symptoms were identified in over 11% of the USA representatives at the Summer Olympic Games in Los Angeles (1984). The observation was confirmed by the studies conducted 12 years later

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at the Olympic Games in Atlanta [3]. In the USA team at the Winter Olympic Games in Nagano (1998), as many as 22% of the athletes had previously been diagnosed with asthma and over 18% had used antiasthmatic medications before [4, 5]. European studies carried out since 2000 have reported a gradual increase in the incidence of asthma and allergy symptoms in athletes [6–9].

When Polish athletes participating in the Olympic Games in Beijing (2008) responded to a questionnaire, 28.4% of them reported at least one symptom of exercise-induced asthma (coughing, shortness of breath, tightening of the chest or wheezing). No differences in asthma symptoms incidence were observed between endurance and non-endurance sports. Clinical evaluation confirmed the diagnosis of asthma in 11.3% of the examined athletes. It is noteworthy that prior to the study inclusion, asthma was diagnosed in 5.9% of the athletes only and 8.6% declared ever taking anti-asthmatic medication, either β_2 -agonists or glucocorticosteroids or leukotriene receptor antagonists [10].

The examination of the Olympic athletes representing Norway, Germany and Spain in Beijing showed an increased risk of symptoms typical of asthma as well as asthma diagnosis by a medical specialist in endurance and water sports athletes [11].

Swimmers represent a group of athletes with a higher risk of the development of exercise-induced asthma symptoms [11–15]. Although swimming is recommended for asthma sufferers to improve their respiratory system functioning, regular swimming may increase the probability of asthma in healthy people. Theoretically, humid and warm environment of most swimming pools should prevent the airway mucosa from drying and cooling. We should bear in mind, however, that exposure to chlorine compounds, mites and mould spores is associated with potential asthma. Skating and cross-country skiing are the kinds of winter sports which are connected with a higher incidence of such symptoms as coughing and dyspnoea. These symptoms are ascribed to the exposure of the airways to adverse conditions or irritating chemical compounds released from the ice [16–21].

Pathogenesis

Asthma is a heterogeneous disease typically associated with a chronic respiratory inflammation which is defined as a syndrome of such respiratory symptoms as wheezing, dyspnoea, chest tightening and coughing which differ in time and intensity and are connected with variable airways obstruction.

Currently discussed pathogenic mechanisms potentially responsible for exercise-induced bronchoconstriction in people who practice high-intensity exercise on a regular basis include [22]:

- osmotic and thermal changes in airways mucosa caused by exercise-induced hyperventilation (osmotic and thermal hypothesis);
- damage to respiratory epithelium;
- increasing severity of the airway inflammation;
- neural activation.

Osmotic and thermal changes to bronchial mucosa are the rationale behind the osmotic and thermal hypotheses which are considered as ‘classical’ ones in the attempts to explain the pathogenesis of EIB in athletes. Increased water evaporation from the mucosa during exercise leads to the increase in the osmolarity of the fluid covering the respiratory epithelium. The changes to osmotic relations result in the lysis of the cells and the release of the mediators including cysteinyl leukotrienes which have strong bronchoconstrictive properties. Furthermore, the airway cooling activates cholinergic receptors, which causes increased tension of bronchial smooth muscles and enhanced fluid secretion in airways. Directly after exercise completion the respiratory tract warming commences and leads to secondary hyperaemia and increased capillary permeability in the bronchial wall.

A rise in the number of inflammatory cells (eosinophils, neutrophils, epithelial cells) has been observed in the respiratory tract of athletes. A large body of evidence has already proven that damage to respiratory epithelium during exercise (particularly in adverse environmental conditions) significantly increases susceptibility to EIB. The conclusions mentioned above were drawn from the analyses of the markers of respiratory epithelium damage (e.g. protein CC16) [23–25]. Unfavourable and harmful environmental conditions for exercise can also contribute to respiratory tract damage and increased susceptibility to EIB. The most spectacular associations were found in the relations between exposure to chlorine compounds (trichloramine) while swimming and the increase in bronchial hyperreactivity (BHR) [12–14, 24–27]. Exposure to dry and cold air while practicing endurance winter sports can be another factor which increases the risk of EIB [16, 28]. Some other studies, however, do not provide results which are compelling enough to significantly associate exercise in adverse conditions with predisposition to EIB. It is suggested that damage to respiratory epithelium occurs only in the presence of BHR symptoms or exercise-induced bronchoconstriction. Consequently, mutual causation and the sequence of the described phenomena are still open to discussion.

The innervation of the respiratory tract is mainly composed of parasympathetic fibres. Stimulation of parasympathetic cholinergic fibres results in bronchoconstriction. In the light of the recent research, high-intensity exercise is thought to magnify para-sympathomimetic activity, thereby increasing the tension of bronchial smooth muscles and, consequently, increasing the probability of EIB. The relationship between BHR and some autonomic nervous system-dependent responses, e.g. perspiration,

tearing, saliva production, have been reported. However, although chronically enhanced parasympathomimetic nervous system activity is observed there are data which do not confirm the correlation between BHR and dysfunctional autonomic regulation. Some authors suggest that autonomic modulation may be involved in BHR development but only when accompanied by the risk of inspiring harmful components of the air [1, 29, 30].

Neurogenic inflammation is also considered in the investigation of EIB pathogenesis [31]. High-intensity exercise elevates the concentration of substance P which is one of the key mediators of neurogenic inflammation. Acetylcholine and nerve growth factor (NGF) have also been put forward as potentially involved in the development of the EIB-provoking inflammation.

Since none of the aforementioned mechanisms fully explains the pathogenesis of EIB, potential interaction of several mechanisms should be taken into account while assessing individual predisposition to exercise-induced respiratory symptoms. The identification of the athletes susceptible to EIB appears to be the key issue here as it may contribute to the improvement of preventive measures.

The observations made within the last 20–30 years indicate that the asthma rate is higher in athletes, especially those practicing endurance sports. The risk of asthma in the athletes with atopy symptoms is several times higher than in healthy population [7].

Diagnostic procedures

Diagnostic procedures in the case of suspected asthma in athletes (when they report exercise-related respiratory problems) should include:

- thorough history including exercise-related problems and comorbidities;
- physical examination with an emphasis on the respiratory system, symptoms of allergic origin and the assessment of any comorbidities which should be taken into account in differential diagnosis;
- assessment of atopic origin (allergy skin tests for inhalants, specific IgE, total IgE) and assessment of the inflammatory process which is typical of asthma (exhaled nitric oxide);
- basic diagnostic tests: morphology with blood smear (eosinophils), C-reactive protein, chest X-ray evaluation;
- functional evaluation of the respiratory system with spirometry, reversible obstruction test, assessment of the reactivity of the bronchial tree in direct challenges (nonspecific bronchoprovocation test with methacholine) – examination taking into account individual indications and contraindication;
- exercise test;
- if the assessment of the cardiovascular system is required, electrographophy (ECG), echocardiography, Holter monitoring of the heart activity and arterial blood pressure (individually selected).

It should be noted that a weak correlation between the symptoms and the results of the pulmonary function test is not uncommon in athletes.

Medical history data

Clinical symptoms of asthma in athletes include coughing (frequently as a sole or dominating symptom), wheezing, chest tightness, 'shortage of breath' or excessive mucus secretion after short, several-minute, continuous exercise. Asthma in athletes can also be manifested by chest pain, 'locker room cough' and lower level of exercise tolerance. Avoiding physical activity and inability to keep up with the peers are also characteristic features [8, 32, 33].

Functional evaluation of the respiratory system is a crucial element in asthma diagnosis. The evaluation should begin with initial spirometry. The procedures which will follow are dependent on the spirometry results and potential obturation [34].

In the case of bronchial tree obstruction, the bronchial reversibility test should be performed (BRT). It should be remembered that normal results of the spirometry test do not exclude reversible obstruction testing and its positive outcomes.

The bronchial reversibility test estimates the ventilation parameters, primarily forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) at 10–20 min after inhalation of 400 μ g salbutamol. The increase in FEV_1 and/or FVC by over 12% and by over 200 ml in comparison to baseline values is regarded as a positive result.

The reversible obstruction test is a method of high specificity and low sensitivity. It identifies negative results in people with normal ventilation indices as well as in patients with significantly decreased indices of ventilation as a consequence of bronchial remodelling. Negative results can also be obtained in patients with inflammatory changes but the ventilation parameters can be improved significantly after several weeks of glucocorticosteroids administration.

The correct performance of BRT depends on careful spirometry and medication administration: 4 single doses of salbutamol ($4 \times 100 \mu$ g) using the inhalation chamber (air completely exhaled, then inhalation of one dose to total lung capacity (TLC), the air held for 5–10 s before exhaling and 30-second intervals between doses). Smaller doses can be applied in children or when side effects (tachycardia, tremor) occur. Salbutamol can be replaced by other drugs e.g. ipratropium bromide ($4 \times 40 \mu$ g). The spirometry test is repeated after 15 min for short-acting β_2 -agonist (SABA) and 30 min for short acting muscarinic antagonist (SAMA), which terminates the evaluation. The test is considered positive at FEV_1 and/or FVC change > 200 ml and 12% of the initial value [35].

When spirometry values fall into the normal range, the diagnostic steps should include the assessment of bronchial hyperactivity by bronchial provocation tests (BPT) [36].

Bronchial hyperreactivity refers to excessive bronchoconstrictive reaction to specific and non-specific stimuli which normally do not cause such a response. Bronchial hyperreactivity can be characterised by respiratory symptoms such as cough, wheeze and dyspnoea and it is assessed by bronchial provocation tests. Clinical practice employs direct and indirect methods. Indirect methods are more specific for asthma whereas direct ones are more sensitive in BHR identification [36].

In direct methods the constriction results from a direct stimulation of the receptors on muscle fibres; methacholine activates muscarinic M3 receptors, histamine activates post-synaptic H1 receptors. The result is expressed as methacholine or histamine concentration which causes FEV₁ decline by 20% in comparison to the baseline value [36].

In indirect methods the bronchoconstriction is induced by degranulation of mast cells and activation of other inflammatory cells (eosinophils) triggered by a substance or factor which releases the mediators responsible for the constriction of bronchial smooth muscles. Indirect methods include the exercise test, hyperventilation test with carbon dioxide-enriched air (EVH) and hypertonic saline or mannitol provocation tests [37, 38].

The International Olympic Committee (IOC) established asthma diagnostic criteria and approval criteria for the use of inhaled anti-asthmatics (including β_2 -agonists) by athletes. The criteria include the symptoms suggestive of asthma in history and a positive outcome of at least one of the following tests [32]:

- positive reversibility test outcome (FEV₁ increased by $\geq 12\%$ and ≥ 200 ml);
- positive exercise test results (temp. 20–25°C, humidity 40–50%) or positive result of eucapnic voluntary hyperventilation with CO₂-enriched air test (EVH) – decline in FEV₁ $\geq 10\%$;
- positive nonspecific bronchoprovocation test with methacholine: PC₂₀ ≤ 4 mg/ml for athletes not taking inhaled glucocorticosteroids or PC₂₀ ≤ 16 mg/ml for athletes taking inhaled glucocorticosteroids > 1 month;
- positive result of the hypertonic saline or mannitol provocation test (decrease in FEV₁ $\geq 15\%$).

Basic diagnostic procedures also include the exercise test after considering the indications and contraindications for such testing. It should be pointed out that the exercise test outcomes are affected by a range of factors, such as the conditions (the air temperature and humidity) and the exercise type (treadmill or cycle ergometer).

The patient qualified for exercise testing should undergo the spirometry test with FEV₁ assessment prior to, directly after and at 1, 5, 10, 15, 30 min after exercise completion (acceptable time modifications according to the patient's status). The test objective is to achieve

75–85% of maximal load and its maintenance for 6–8 min. Seven–nine min is the optimal duration of the exercise test. Maximal load is defined as the exercise which does not cause further increase in oxygen intake. The type of exercise load protocols depends on the laboratory, the patient's age, fitness level and comorbidities. Common guidelines, however, recommend that the patient should breathe through the mouth (clip on the nose) with the air temperature of 20–25°C and humidity below 50%.

The exercise load should be increased and lead to 40–60% of predicted maximal voluntary ventilation within the first 2–3 min (initial value: FEV₁ $\times 35$) or 80–90% of the predicted maximal heart rate (HR = 220 – age in years) [39]. Nevertheless, in well-trained athletes the recommended exercise load values may be insufficient. In justified cases, the conditions of the given athlete's sports discipline should be considered as the exercise testing venue [40].

Exhaled nitric oxide assessment (F_{ENO}) is an easy and non-invasive diagnostic study. An increased expression of inducible nitric oxide synthase and elevated F_{ENO} level have been demonstrated in asthma sufferers. F_{ENO} is an inflammation-sensitive marker which responds quickly to implemented treatment as well as to disease exacerbation and in asthmatic patients it correlates well with the indices of the inflammatory process connected with eosinophilic infiltration. The contribution of F_{ENO} measurements in monitoring the treatment with inhaled steroids should not be underrated [41, 42]. The identification of increased exhaled nitric oxide values (over 25 ppb – mild, over 35 ppb – moderate, over 50 ppb – high) in athletes displaying typical exercise-induced asthma symptoms has a high predictive value in asthma diagnosis.

Each case should be analysed individually and in case of diagnostic doubts, indistinctive symptoms or no desirable treatment results, differential diagnosis is advisable [32, 33] and should include:

- cardiovascular diseases (heart diseases, ischemic heart disease, arterial hypertension), respiratory diseases (eosinophilic pulmonary diseases, chronic bronchitis, tuberculosis);
- chronic pulmonary embolism;
- chronic sinusitis and inflammation of nasal mucosa;
- exercise-induced laryngeal dysfunction (abnormal larynx response to physical exercise) manifested by inspiratory dyspnoea and exercise-induced inspiratory stridor. The symptoms occur during exercise and subside 5 min after exercise completion;
- gastroesophageal reflux disease, which may be the underlying cause of exercise-induced respiratory symptoms and may coexist with vocal fold dysfunction;
- exercise-induced hyperventilation (a pseudo-asthma syndrome), which may be connected with hypocapnia and potentially with exercise-induced disturbances in respiratory homeostasis;

- exercise-induced anaphylaxis. Predisposing factors of exercise-induced anaphylaxis include: food consumption (wheat 57%, shrimps 17%, crabs, nuts, grapes, buckwheat, fish, tomatoes, celery, egg white) most commonly within the first 4 h before exercise, acetylsalicylic acid (ASA), non-steroid anti-inflammatory drugs (NSAIDs), alcohol, fatigue, infection, stress. American studies reported that 5–15% of anaphylaxes in children were induced by exercise.

Treatment

Treatment of asthma in athletes should be provided in accordance with the current guidelines on asthma management preserving the specific needs of asthmatic patients. The guidelines have been developed by the Global Initiative for Asthma and they describe the aims of successful treatment as follows:

- achievement and maintenance of symptoms control;
- prevention of exacerbation;
- maintenance of the respiratory function at close to normal parameters;
- maintenance of everyday activity including physical exercise.

The objective of asthma management in athletes includes reduced adverse impact of exercise on the respiratory system, which significantly affects exercise capacity and sports achievements.

On the implementation of asthma treatment one should remember about diverse character of the disease which is closely related to the pathomechanism of respiratory inflammation. Varied asthma phenotypes can be distinguished in athletes, some examples being atopic asthma, accompanied by other allergies, or exercise-induced respiratory symptoms and bronchial hyperreactivity (BHR) unrelated to allergy but related to

the specific environment [43]. Respiratory tract inflammation is the primary cause of the disease symptoms, therefore early anti-inflammatory intervention with inhaled glucocorticosteroids is crucial and indispensable in asthma management in athletes. Bronchodilators (SABA, long-acting β -agonists (LABA)) should not be applied as the sole medication. The treatment must be adjusted to the symptoms severity. In order to fully control the disease and to reduce the risk of asthma exacerbation, several intensity degrees of asthma therapy have been suggested [42].

Inhaled glucocorticosteroids are basic medicines in chronic therapy yet they are too infrequently applied by athletes [44]. They should be used in appropriate doses at the earliest stage possible.

Doses of inhaled glucocorticosteroids are determined by the degree of symptoms severity. Daily doses of inhaled glucocorticosteroids according to GINA 2017 are shown in the Table 1.

Occasionally, for various reasons, inhaled glucocorticosteroids are less effective in asthma control in competitive athletes. Hoshino *et al.* reported ineffectiveness of therapy with inhaled glucocorticosteroids in 16.3% of 80 asthmatic athletes [45].

Apart from anti-inflammatory activity, glucocorticosteroids reduce the dose of required β -mimetics, diminish β -mimetics tolerance and, what is of particular value, decrease bronchial reactivity (to exercise, cold, allergens). It may be concluded that when SABA application is necessary more often than twice a week, the therapy should include regular inhaled glucocorticosteroids applied in small doses. Infrequently, in case of asthma exacerbation, glucocorticosteroids are applied orally.

Mild symptoms can be managed by leukotriene receptor antagonists (LTRAs) (montelukast). Antileukotriene drugs weaken exercise-induced bronchoconstriction

Table 1. Daily doses of inhaled glucocorticosteroids according to GINA 2017

Medication	Daily dose [μ g]		
	Low	Medium	High
Betamethasone dipropionate (CFC – suspension)	200–500	> 500–1000	> 1000
Betamethasone dipropionate (HFA – solution)	100–200	> 200–400	> 400
Budesonide (DPI)	200–400	> 400–800	> 800
Ciclesonide (HFA – solution)	80–160	> 160–320	> 320
Fluticasone furoate (DPI)	100	N/A	N/A
Fluticasone propionate (DPI)	100–250	> 250–500	> 500
Fluticasone propionate (HFA – suspension)	100–250	> 250–500	> 500
Mometasone furoate	110–220	> 440–880	> 880
Triamcinolone acetonide	400–1000	> 1000–2000	> 2000

and protect against environmental contaminants [46, 47]. Chronic application of antileukotriene drugs have been proven to be effective in prevention of sudden exercise-induced dyspnoea [48, 49]. Reduction of the applied dose of inhaled glucocorticosteroids may be facilitated by inclusion of LTRA. Similar effects are produced by allergen immunotherapy applied in patients allergic to house dust mites.

β_2 -Mimetics

Owing to their quick and effective bronchodilating properties, β_2 -mimetics are the most frequently used medications in asthma management. They prevent sudden dyspnoea when applied 5–10 min prior to exercise. Short-acting β -agonists and long-acting β -agonists are used in asthma management (Table 2).

Table 2. Short-acting β -agonists (SABA) and long-acting β -agonists (LABA) are used in asthma management

Short-acting β -agonists:	
Bitolterol	– Tornalate
Fenoterol	– Berotec
Isoprenaline/isoproterenol	– Isuprel
Levosalbutamol/levalbuterol	– Xopenex
Orciprenaline/metaproterenol	– Alupent
Pirbuterol	– Maxair
Salbutamol/albuterol	– Ventolin
Terbutaline	– Bricanyl
Long-acting β -agonists:	
Arformoterol	– Brovana
Bambuterol	– Bambec, Oxeol
Clenbuterol	– Dilaterol, Spiropent
Formoterol	– Foradil, Oxis
Salmeterol	– Serevent
Ultra-long acting β_2 -agonists (ultra-LABA):	
Abediterol	
Carmoterol	
Indacaterol	– Arcapta Neohaler (U.S.), Onbrez Breezhaler (EU, RU)
Olodaterol	– Striverdi Respimat
Vilanterol:	
with umeclidinium bromide	– Anoro Ellipta
with fluticasone furoate	– Breo Ellipta (U.S.), Relvar Ellipta (EU, RU)

The above-mentioned medications are not recommended in monotherapy as they can increase the risk of acute dyspnoea [50]. When pro re nata (PRN) SABA application is required more often than 2 times per week, inhaled glucocorticosteroids in minimal doses should be included in the therapy.

When applied systematically as the exclusive medication, β -adrenergic agonists increase bronchoconstrictive responsiveness of airways to exercise and allergens, augment BHR (if they are not applied prior to exercise) and decrease their effectiveness when applied PRN in sudden dyspnoea [51].

Regular application of β_2 -agonists in monotherapy can also lead to the drug tolerance which will reduce their protective and bronchodilatory properties. β -Mimetics applied in therapeutic doses do not affect the athlete's exercise performance [51].

Anticholinergic drugs can be selected out of other bronchodilators and applied in specific asthma patients. They are of particular use in the athletes who display increased parasympathetic tone [30].

Atopic athletes who suffer from rhinitis or conjunctivitis triggered by exposure to allergens should use antihistamines. Allergen immunotherapy is a method of choice for people allergic to pollen and home dust mite. Desensitization modifies the course of disease, relieves the symptoms, prevents new allergies and reduces the dosage of applied inhaled glucocorticosteroids [52, 53].

The available literature reports protective properties of cromones in exercise-induced bronchoconstriction [54]. Yet, they are infrequently used since other, more effective and rapidly activated and long-lasting agents, are more easily available.

One must not forget about successful treatment of concomitant diseases including upper respiratory tract diseases and, so called, common colds [55].

The usefulness of vitamin D application and supplementation with omega-3 poly-unsaturated fatty acid (PUFA), colostrum, probiotics and selected antioxidants is subject to discussion [56, 57].

It is extremely important that asthma sufferers should be educated on the correct drug application (inhalation technique), the recognition of the disease exacerbation and appropriate modification to their therapy. The patients should be provided with the treatment plan and their comprehension and compliance should be controlled regularly, particularly at the onset of the therapy. Regrettably, a large number of athletes do not comply with medical recommendations [58].

Non-pharmacological treatment

There are numerous factors which have an influence on undisturbed respiratory functioning and they include, first and foremost, environmental factors such as air temperature, humidity and quality in terms of its content of allergens, irritating agents and contaminants.

Therefore, along with pharmacological treatment, asthma sufferers, and athletes in particular, should reduce their exposure to the aforementioned agents.

Exercise should be performed only when asthma is stable and well controlled. Exercise should always be preceded by a warm-up and, so called, 'cold start' ought to be avoided.

Exercising in the company of another person is advisable. It is also recommended that the exercise intensity should be gradually reduced towards the end of training (opposite to warm-up).

Fluids should be frequently replenished in order to avoid dehydration.

When exercising in low temperatures, the use of the protective mask should be considered.

The air warming mask proves effective in prevention of exercise-induced bronchoconstriction triggered by cold air. It enhances humidity of inhaled air and prevents water loss while breathing [59]. Good interpersonal communication between the athlete and his coach and doctor plays an extremely important role in the maintenance of good athletic performance.

To sum up, asthma treatment in athletes is aimed at achieving full control of the disease by self-control, education, monitoring the environmental conditions and by adaptive pharmacotherapy.

Asthma treatment and doping

Correctly performed functional testing allows to confirm asthma diagnosis, select pharmacotherapy and monitor treatment. However, the medications used in asthma therapy, based on β_2 -adrenergic agonists and glucocorticosteroids, can also be used for doping purposes. Apart from controlling the basic disease and enabling the continuation of athletic career, the management of asthmatic athletes should also warrant equal opportunities in competition with healthy athletes without the risk of doping suspicions [60]. The opinions on the competition between asthmatic and healthy athletes are still divided. The opinion that the application of some medications by asthma athletes is nothing but doping used for performance enhancement without the risk of disqualification is not unique in the medical circles, too. On the other hand, there have been reported cases of athletes who threatened their health and life by giving up pharmacotherapy, including anti-asthmatics, for fear of suspicions of doping. What is of key importance here is the knowledge of current anti-doping regulations and asthma treatment methods which are permitted by the World Anti-Doping Agency (WADA).

The list of substances and methods prohibited in sport is one of the prime documents of the World Anti-Doping Programme. Since 2004 WADA has published an annually updated list of methods and substances grouped in three categories i.e.:

Table 3. List of substances and methods prohibited in sport in 2018*

Substances and methods prohibited at all times (in- and out-of-competition):
S0. Non-approved substances
S1. Anabolic agents
S2. Peptide hormones, growth factors, related substances and mimetics
S3. β_2 -agonists
S4. Hormone and metabolic modulators
S5. Diuretics and masking agents
M1. Manipulation of blood and blood components
M2. Chemical and physical manipulation
M3. Gene doping
Substances and methods prohibited in-competition (in addition to categories S0 to S5 and M1 to M3 defined above, the following categories are prohibited in-competition):
S6. Stimulants
S7. Narcotics
S8. Cannabinoids
S9. Glucocorticoids
Substances prohibited in particular sports:
P1. β -Blockers

*Updated and full prohibited list is available on WADA website (www.wada-ama.org).

- substances and methods prohibited at all times (in- and out-of-competition);
- substances and methods prohibited in competition;
- substances and methods prohibited in particular sports (Table 3).

Each athlete has the right to be treated with medications which contain substances that are on the prohibited list. In most cases, however, this is possible only after the formal approval, i.e. after Therapeutic Use Exemption (TUE) has been granted. For that purpose the following criteria must be fulfilled:

- The athlete would experience a significant impairment to health if the prohibited substance or method were to be withheld in the course of treatment.
- The therapeutic use of the prohibited substance or method is unlikely to produce additional enhancement to performance other than that which might be anticipated by a return to normal health following the treatment of a legitimate medical condition.
- There is no reasonable alternative to the use of otherwise prohibited substance or method.

According to anti-doping regulations, however, therapy with some medications which contain substances classified as doping agents is not prohibited. The WADA

permits the application of some pharmaceutical substance for medical purposes.

Compounds from two classes on a list of prohibited substances and methods are applied in asthma treatment: β_2 -mimetics (category S3) and glucocorticosteroids. Clenbuterol is an exception as, although it is a β_2 -mimetic from a pharmacological standpoint, it has been included by WADA in a category of anabolic agents (S1). In accordance with current WADA regulations, athletes are permitted to use inhaled glucocorticosteroids and some β_2 -mimetics also as inhalations, i.e. salbutamol (maximum 800 μg within 12 h), formoterol (maximal daily dose: 54 μg) and salmeterol (maximum 200 $\mu\text{g}/\text{day}$). The use of other drug forms (if available) containing the above-mentioned substances or any other medications with β_2 -mimetics as well as preparations with glucocorticosteroids applied systemically (orally, intravenously, intramuscularly or per rectum) requires Therapeutic Use Exemption (TUE). The WADA also established that the presence in urine of salbutamol in excess of 1000 ng/ml or formoterol in excess of 40 ng/ml is not consistent with the therapeutic use of the substance and will be considered as an Adverse Analytical Finding (AAF) unless the athlete proves, through a controlled pharmacokinetic study, that the abnormal result was the consequence of a therapeutic and permitted dose by inhalation [61]. Such controlled studies allowed to overrule the suspicions of anti-doping rules violation in many cases, especially the cases of inhaled glucocorticosteroids [62]. Nevertheless, it should be strongly emphasised that although formally permitted, the use of preparations of salbutamol, formoterol and salmeterol should be limited to therapeutic applications only.

The list of substances and methods prohibited in sport is an open list. The majority of categories include only examples of doping substances as well as the note

that other substances with a similar chemical structure or similar biological effects are also prohibited.

In 2004–2016, WADA published annual versions of the prohibited list with a description of the group of β_2 -agonists accompanied by brief information that all the substances from the group are prohibited, including all the optical isomers (e.g. d- and l-) if they occur. The prohibited list which came into effect on 1 January 2017 listed 11 examples of prohibited β_2 -mimetics for the first time. It is common knowledge, however, that this group of compounds is composed of significantly more substances (Table 4) [63].

The WADA specified the examples of prohibited glucocorticosteroids for the first time on the list of 1 January 2018 and these included: betamethasone, budesonide, cortisone, deflazacort, dexamethasone, fluticasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone.

Such a significant change, in comparison with the previous years, was caused by an increasing number of new medications based on a wider range of β_2 -mimetics on the one hand, and by the problem of higenamine (also known as norcoclaurine) as an ingredient in dietary and sports supplements on the other. The WADA's intention was to warn against the use of newly appearing anti-asthmatic medications but also to attract attention to plant-derived dietary supplements which may contain doping agents from β_2 -agonists. Such ingredients are often omitted in the product description on the label and their consumption may not only result in positive anti-doping tests but also harmful side effects [64, 65]. It should be underlined that it is the athletes' responsibility to make sure that the medication or the supplement they use does not contain prohibited substances.

Summary

Recently the prevalence of asthma and allergies has been increasing both in general population and in elite athletes. High-intensity exercise in adverse environmental conditions (cold air, humidity, contamination, allergens) may increase the risk of EIB and asthma symptoms in athletes. Asthma and allergies in elite athletes are largely underdiagnosed, which may result from misleading interpretation of exercise-induced symptoms and poor awareness among the athletes, coaches as well as medical staff, of the impact asthma and allergies have on sports performance. Apart from 'classical' hypotheses (osmotic and thermal ones) concerning the pathogenesis of exercise-induced bronchoconstriction and asthma, the involvement of other mechanisms is currently being discussed and these mechanisms include epithelium damage, inflammatory process exacerbation induced by regular, high-intensity exercise as well as increased parasympathomimetic activity in the respiratory tract. In case of suspected asthma in athletes, the diagnostic procedures should include

Table 4. Examples of common β_2 -mimetics

Bambuterol	Indacaterol*	Ritodrine
Brombuterol	Isoxsuprine	Salbutamol*
Cimaterol	Mabuterol	Salmeterol*
Cimbuterol	Mapenterol	Terbutaline*
Clenbuterol#	Olodaterol*	Tulobuterol*
Clenpenterol	Pirbuterol	Vilanterol*
Fenoterol*	Procaterol*	Zilpaterol
Formoterol*	Ractopamine	
Higenamine*	Reproterol*	

#The substance classified by WADA as an example of doping substances in the category of anabolic agents (S1), *the substance classified by WADA as an example of doping substances in the category of β_2 -mimetics (S3).

history taking, physical examination, atopic origin assessment and functional evaluation of the respiratory system. Along with good history taking, the diagnosis of asthma should rely on the positive outcome of at least one of the following tests: reversibility test, exercise test or positive result of eucapnic voluntary hyperventilation with CO₂-enriched air test, nonspecific bronchoprovocation test with methacholine, hypertonic saline or mannitol provocation test. The aim of successful asthma management includes: achievement and maintenance of symptoms control, prevention of exacerbation, maintenance of the respiratory function within normal range of parameters. Asthma is a respiratory tract inflammation so inhaled glucocorticosteroids should be applied as the basic medication in chronic therapy and β -adrenergic antagonists should never be used as monotherapy. The treatment of asthma in athletes should always take into account current anti-doping regulations. According to WADA regulations, treatment of diagnosed asthma in athletes is not considered as doping, contrary to any attempts to use anti-asthmatic medication in healthy athletes.

Conflict of interest

The authors declare no conflict of interest.

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