

# Asthma in athletes and the use of asthma treatment

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### Abstract

Asthma is a common disease of civilization characterized by a triad of symptoms: coughing, shortness of breath, and wheezing. We know how to diagnose patients with asthma, and the use of provocation tests can accurately determine how big the problem is. Treatment of patients with diagnosed asthma is highly individual. It is based on patient's education and knowledge of the disease, assessment of the degree of symptoms, possibility of medical treatment and monitoring the patient during the course of drug therapy. The aim of the therapy is to control symptoms associated with asthma. During frequent, intense and prolonged physical exercise at a swimming pool, bronchial shrinking under the influence of the vagus nerve and the hyperventilation of the lower respiratory tract may occur, which are closely related to the changes of humidity and temperature. As a result, a number of irritant effects of chlorine may develop, which can lead to severe asthmatic reactions [2, 4, 7, 9, 10, 12]. This study is a review paper on asthma and exercise-induced asthma in professional swimmers. The first part of the paper is a holistic representation of various aspects of asthma: factors influencing its course, development, diagnosis and therapeutic management. In the second part, the authors discuss the impact of swimming pool water disinfection and hyperventilation on the risk of asthma in swimmers, and to what extent the treatment of asthma in swimmers and professional athletes may count as illegal doping in view of present-day anti-doping regulations.

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### What is already known on this topic?

Asthma is a common global-scale disease that occurs in children and adults. It is considered a disease of civilization of the 20<sup>th</sup> century. Bronchial asthma factors can be divided into environmental and genetic. The former include viral infections, allergens, occupational hazards, smoking, air pollution and medicaments. The genetic factors which are significant for the course of asthma consist of incorrect immune responses to small doses of allergens. Genetic predispositions may contribute to the improper function of beta-2-adrenergic receptors by reducing their activity and – in consequence – causing disturbed tonicity of bronchial muscles due to the dominance of the parasympathetic nervous system controlling muscle contraction. Asthma diagnosis is based on medical history, clinical manifestations and pulmonary function tests. Asthma treatment is aimed at the limitation of breathing disorders and ensuring comfort in performing activities of daily living. In athletes, asthma treatment is aimed at ensuring performance of high intensity without asthmatic symptoms and with strict adherence to WADA regulations. Athletes with asthma use inhaled beta-2-blockers and corticosteroids according to TUE specifications.

Asthma is a common global-scale disease that occurs in children and adults. It is considered a disease of civilization of the 20<sup>th</sup> century. The term *asthma*

comes from the Greek word for “panting”. It is a chronic inflammatory disease of the lower airways. Its main triad of symptoms includes coughing, wheezing and shortness of breath, while other symptoms may be bronchospasm, chest tightness, mucous edema, and appearance of sputum. The constriction of the airways, due to inflammation-related increasing tone of bronchial muscles caused by IgE antibodies and immune system cells that commence a pathological response, varies in individuals. Asthma symptoms may also vary in terms of their intensity and severity affecting activities of daily living [1].

Bronchial asthma factors can be divided into environmental and genetic. The former include viral infections, allergens, occupational hazards, smoking, air pollution and medicaments. Pharmaceuticals that may cause asthma are, first of all, non-steroidal anti-inflammatory drugs (NSAIDs), in particular, aspirin. Other factors include common substances of animal and vegetable origin as well as substances causing immune responses. The most important factors producing asthma symptoms are house dust mites, pet allergens, and cockroach, fungi, mold, yeast and pollen allergens [2, 3].

The genetic factors which are significant for the course of asthma consist of incorrect immune responses to small doses of allergens. These responses lead then to the oversecretion of IgE antibodies against these allergens. Individuals with atopy are hyperallergic to substances, otherwise harmless to the healthy population. Clinical research shows that the risk of asthma is 40% to 80% higher in genetically predisposed individuals, for example, in asthmatic parents the risk of asthma incidence in their children is 3 to 6 times greater. Researchers have not described a single gene responsible for atopy, but they have identified over 100 genes responsible for development of asthma. Genetic predispositions may contribute to the improper function of beta-2-adrenergic receptors by reducing their activity and – in consequence – causing disturbed tonicity of bronchial muscles due to the dominance of the parasympathetic nervous system controlling muscle contraction.

Exercise Induced Asthma (EIA) is an inflammatory condition in which constriction of the lower airways and other asthma symptoms are induced by physical exercise in individuals with diagnosed bronchial asthma. According to various studies the EIA occur in 70% to 90% in asthma patients [2].

Exercise Induced Bronchospasm (EIB) is a transient bronchoconstriction manifested by coughing, wheezing, chest tightness and pain during and after intensive physical exercise in people with no asthma. The EIB, according to different authors, occurs in 3% to 13% of the general healthy population, and in 10% to 20% of high-performance athletes. The EIB pathomechanism has not been satisfactorily explained; however, two types of EIB pathological mechanisms can be distinguished: osmotic and vascular [3].

The osmotic hypothesis assumes that the EIB occurs due to reduced hydration of the lower airways and pulmonary alveoli caused by pulmonary hyperventilation during exercise. Its consequence is increased mucus density, which stimulates the nerve endings of the mucous membrane, breakdown of mast cells, and the release of inflammatory mediators, all contributing to bronchoconstriction [3].

The vascular hypothesis assumes that increased pulmonary ventilation during exercise (about 200 L/min) causes the loss of heat in the airways. The cooling brings about a reflexive expansion of blood vessels and their hyperemia. Such a vascular response aims to warm the linings of the bronchial tree followed by a constriction of the airways [2, 4].

The bronchial asthma diagnosis includes the patient's medical history considering the incidence of the characteristic triad of symptoms as well as pulmonary function tests. Spirometry allows the measurement of such parameters as forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), i.e. the volume of air that can forcibly be blown out after full inspiration. When FEV1 is below or equal to 80%, or the FEV1 to FVC ratio is lower than 70%, such data provide information about the degree of airway obstruction [4, 5].

If the function tests fail to reveal asthma, but the clinical image indicates its incidence, a non-specific bronchoprovocation challenge with incremental concentration of inhaled substance, e.g. histamine, metacholine, adenosine or aspirin, should be carried out. The test result is positive when FEV1 drops below 20% than the value after inhalation [6].

If there are no asthma symptoms evoked by bronchoprovocative substances, allergic tests should be conducted that will enable a provocation challenge using a specific allergen producing a positive result of a skin test [6].

Another diagnostic test is the assessment of reversibility of airflow obstruction following the administration of a drug dilating the airways. The result of the test is then compared with the FEV<sub>1</sub> result. If it is above 200 ml, i.e. 12%, the result of the bronchial obstruction reversibility test is considered positive [4, 7].

Diagnosis of exercise-induced asthma involves a spirometric examination immediately, 5, 10, and 20 minutes after exercise on a cycloergometer or a treadmill. A participant below 25 years of age should attain from 75 to 80% HR max within 1-2 min and maintain this rate from 6 to 8 minutes. The test result is positive if the spirometry after exercise reveals a 10% drop in FEV<sub>1</sub> compared to baseline [4].

Athletes who are not able to take the test in laboratory conditions in order to obtain the appropriate level of pulmonary ventilation to evoke a bronchoconstriction, can take the challenge using cold air at -20°C to ensure test specificity.

The exercise test is not recommended when FEV<sub>1</sub> is below 60%; in patients with cardiovascular diseases; when participants undertook intensive training about 4 hours before the test; or when participants took drugs regulating bronchial reactivity from 4 to 96 hours before the test [4, 8].

Other types of asthma diagnostic tests in athletes are bronchoprovocation challenges with the use of 4.5% hypersmolar saline solution, or mannitol and eucapnic voluntary hyperventilation (EVH). The first type consists of inhaling a specified dose of the substance in order to elevate bronchial osmolarity, release inflammatory mediators and narrow the lower airways. Before the challenge and after administration of the solution pulmonary function tests should be carried out. The challenge is interrupted when FEV<sub>1</sub> falls below 15% of baseline, or after administering the maximal dose (22 ml) of the substance. The body's reactions depend of the dose evoking the FEV<sub>1</sub> drop and obstructive alterations. They can be divided into mild (6 ml), moderate (from 2.1 ml to 6.0 ml), and severe (2.1 ml and below) [9].

The mannitol bronchoprovocation challenge is analogous to the hypersolar saline solution challenge. Mannitol's activity is identical, i.e. it increases bronchial osmolarity and causes mast cell degranulation, i.e. elevates the inflammatory state and – in consequence – constriction of the lower airways. During the challenge mannitol is inhaled until the dosage reaches 635 mg, or when FEV<sub>1</sub> drops below 15% of baseline [10].

The EVH consists of breathing dry air with 4.9% of carbon dioxide at a very high ventilation rate. The challenge can follow two protocols: progressive and constant. According to the progressive protocol a participant should breathe for 3 minutes at 30%, 60% and 90% of their own maximal voluntary ventilation. This test is used in patients with diagnosed bronchial asthma. The constant protocol is used in individuals with undiagnosed asthma and consists of breathing for 6 minutes at 80% of their maximal voluntary ventilation. During the EVH challenge a drop in the post-test FEV<sub>1</sub> (compared with baseline values) of more than 10% is considered positive. An FEV<sub>1</sub> drop between 10% and 19.9% is considered mild, between 20% and 29.9% moderate, and above 30% severe. The eucapnic voluntary hyperventilation test is regarded as the “gold standard” for diagnosing exercise-induced asthma since the testing conditions and results allow for more accurate standardization than any other, sport-specific challenges [11].

The above tests are characterized by their high sensitivity and specificity in diagnosis of bronchial and exercise-induced asthma, and their diagnostic criteria adhere to the IOC and WADA guidelines [6, 10].

Treatment of patients with diagnosed bronchial asthma is individualized and usually comprises of informing patients about the disease, its severity, possible medical procedures and controlling the patient's condition during the pharmacological therapy. Patients undergo regular checkups, the accuracy of drug therapy is constantly verified, and the administration of drugs is gradually reduced. Two types of asthma treatment drugs can be distinguished: long-acting and short-acting. The former include glucocorticosteroids, antileukotrienes, methylxantines, monoclonal anti-IgE antibodies and beta-2-adrenergic agonists. The latter aim to alleviate sudden attacks of breathlessness and include inhaled beta-2-adrenergic agonists, and anticholinergics for patients with adverse drug reactions to beta-2-adrenergic agonists [4].

The above theoretical considerations can be exemplified by cases of competitive swimmers receiving asthma therapy with regard to anti-doping regulations, and by the question of prevention of asthma exacerbations during swimming training. More specifically, two important research issues should be addressed:

1. What are the effects of swimming pool water disinfectants and pulmonary hyperventilation on the risk of asthma incidence in competitive swimmers?
2. To what extent can asthma treatment in competitive swimming be considered illegal doping?

Due to its beneficial effects on the respiratory system physical exercise in warm and humid air, e.g. swimming, is recommended to patients with bronchial asthma. However, competitive swimmers in indoor and outdoor pools are often exposed to chlorine pool water disinfectants such as sodium hypochlorite and chlorinated isocyanuric acid. The reactions of these disinfectants with substances in the water lead to the production of trichloromethane or trichloronitromethanes that are harmful to the eyes, skin and airways. During frequent, long-lasting and intense physical exercise in a swimming pool the bronchi may constrict due to the dominance of the vagus nerve and hyperventilation combined with changes in ambient humidity and temperature. In result, the irritating effect of the chloramines may lead to an exacerbated asthmatic reaction [2, 4, 7, 9, 10, 12].

Asthmatic symptoms in the upper and lower airways occur more often in experienced athletes who train intensively in adverse respiratory conditions (e.g. high air concentration of chloramines) for a long time. The symptoms in swimmers' upper airways include constriction of the nasal mucosa leading to airflow obstruction, catarrhal inflammation, itching and chronic rhinitis. The disturbances in the lower airways involve bronchoconstriction, wheezing, shortness of breath, chest tightness, extensive mucus secretion and coughing. Due to all these symptoms appearing during intensive training the quality of life and competitive level of experienced swimmers deteriorate significantly [13, 14, 15].

Asthma and bronchial hyperresponsiveness can develop in experienced competitive swimmers exposed for a long time to harmful substances. Regular and intense training in anaerobic conditions and prevalence of the medical condition in a family member are conducive to chronic inflammations of the airways. Studies on the effects of chlorine compounds on the respiratory system also reveal that competitive swimmers may often suffer from conjunctivitis, chondritis and exercise-induced bronchoconstriction (EIB), but much more rarely from airways inflammation [6, 15, 16].

Not only does the pool water contain substances causing pathological mechanisms, but also the air in the swimming pool is saturated with nitrogen trichloride, which causes so-called occupational asthma in water rescuers and swimming instructors who spend long hours at the pool inhaling hazardous substances. The researchers indicate the presence of exacerbated

symptoms such as the pink eye, cold, post-nasal drip, loss of voice, and – in consequence – chronic inflammation of the airways [17, 18, 19].

Asthma treatment in competitive swimmers should be based on prevention of exposure to chlorine substances. Non-chlorine water disinfecting or conditioning factors should be used instead, e.g. ozone, or silver or copper compounds, as well as new ventilation-enhancing techniques that would eliminate asthma factors. The level of nitrogen trichloride should be constantly monitored, fresh air supply should be ensured and the proper air and water temperature should be maintained. Swimmers should be properly hydrated and adhere to a low-sodium diet. Also athletes with symptoms of exercise-induced or allergic asthma should use pre-training warm-up and intermittent exercises to reduce EIB and increase the blood flow in the bronchi, which will ensure the removal of chemical substances producing adverse symptoms.

Medical treatment using drugs considered doping substances must strictly follow the regulations of the World Anti-Doping Agency (WADA). This is to ensure that pharmaceuticals used by athletes are prohibited substances. Medicines taken by athletes have anabolic effects and may enhance exercise performance. An athlete receiving pharmaceutical treatment must apply to WADA for a therapeutic use exemption (TUE) that will give him or her authorization to take the prohibited substances for medical purposes.

An athlete may be granted a TUE, if (and only if) he/she can show that each of the following conditions is met:

1. The prohibited substance or prohibited method in question is needed to treat an acute or chronic medical condition, such that the athlete would experience a significant impairment to health if the prohibited substance or prohibited method were to be withheld.
2. The therapeutic use of the prohibited substance or prohibited method is highly unlikely to produce any additional enhancement of performance beyond what might be anticipated by a return to the athlete's normal state of health following the treatment of the acute or chronic medical condition.
3. There is no reasonable therapeutic alternative to the use of the prohibited substance or prohibited method.
4. The necessity for the use of the prohibited substance or prohibited method is not a consequence, wholly or in part, of the prior use (without a TUE) of a substance or method which was prohibited at the time of such use.

According to the current anti-doping regulations competitive swimmers are allowed to use certain inhaled beta-2-andronergic agonists, e.g. formoterol, salbutamol, salmeterol, terbutalin and inhaled corticosteroids (ICS), in dosages precisely determined in the TUEs. In such cases properly treated and controlled asthma is not detrimental to the swimmer's health, and the dosages of substances defined by WADA effectively suppress the symptoms of the disease [6, 8, 10].

Research shows that the use of the above substances by healthy athletes does not enhance endurance and speed, with the exception of orally administered salbutamol, which enhances strength. These substances do neither enhance aerobic or anaerobic performance [19, 20, 21]. In summary, bronchial asthma is a chronic inflammatory state of the lower airways manifested by breathlessness, coughing and bronchial obstruction. Exercise-induced symptoms are usually called transient bronchoconstriction. Asthma diagnosis is based on medical history, clinical manifestations and pulmonary function tests. Asthma treatment is aimed at the limitation of breathing disorders and ensuring comfort in performing activities of daily living. In athletes, asthma treatment is aimed at ensuring performance of high intensity without asthmatic symptoms and with strict adherence to WADA regulations. Athletes with asthma use inhaled beta-2-blockers and corticosteroids according to TUE specifications. From the physiological standpoint there are no grounds to include these substances into the WADA Prohibited List, since any evidence of purposeful enhancement of performance in competitive athletes indicates performance improvement, e.g. endurance and speed, only in athletes with asthma. No study has indicated performance-enhancing effects of these substances in healthy athletes.

#### What this paper adds?

The present study is a review paper on the pathological mechanisms of bronchial and exercise-induced asthma in competitive swimmers. The first part discusses factors affecting asthma course, development, diagnosis, and treatment. The second part of the paper analyzes the impact of pool water disinfectants and hyperventilation on the risk of asthma prevalence in competitive swimmers. The authors also discuss to what extent asthma treatment in competitive swimmers can be considered illegal doping in view of anti-doping regulations.

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