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Physical exercise-induced bronchial asthma in athletes: unsolved problems and possibilities of prophylaxis and therapy (review)

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Summary

Physical exercise-induced bronchial asthma is a disease, which is one of the reasons for the removal of athletes from training and sports. At the same time, if treatment is adequate, athletes can attain high results. The algorithm of physical exercise-induced asthma diagnostics should include, in addition to the purely medical standard examination, the testing under conditions of loads modelling and in the course of natural training process for the estimation of variations in the peak rate of expiration. The prophylaxis of bronchoconstriction attacks under physical loads in athletes with this disease must be based on their teaching: keeping a diet, obligatory intense warm-up load, and use of pharmacological drugs, including those with the metabolitotropic, immunomodulative, and energotonic actions. When having physical exercise-induced asthma, the therapeutic approach must obligatorily be considered that a significant part of bronchodilators is referred to the substances forbidden in sport and will be built on this basis. At present, there exist the targeted methodologies of prophylaxis and treatment of this disease in athletes with the use of allowed medicinal agents such as antileucotrienes. They are permitted for the application to young and adult athletes and give a high therapeutic effect with insignificant number of side phenomena.

Keywords: *physical exercise-induced bronchial asthma, sport, prophylaxis, treatment, bronchodilators, antileucotrienes, doping.*

Introduction

At the present time, it is necessary to distinguish, terminologically and etiologically, exercise-induced bronchospasm (EIB) or bronchial obstruction arising as a response of a person with normal function of lungs without loads to a physical load and properly physical exercise-induced asthma (EIA), which is the hard breathing in a patient with asthma during and after a physical load. EIA is one of the manifestations of hypersensitivity of respiratory tracts, rather than a particular form of asthma (Novik, 2007). The use of the most modern immunological and instrumental methods of studies allows one to unambiguously conclude that physical load is one of the most important nonimmunological and nonpharmacological stimuli that lead to the development of acute spasm of respiratory tracts in patients with bronchial asthma.

In his interview given to the journal “Championship” on July 8, 2015, the doctor of Russia’s national team Il’ya Melekhin presented

some interesting facts. In particular, he indicated that “...bronchial asthma met in the winter kinds of sport became the talk of the town due to, in the first turn, Scandinavian athletes. The first “open” asthmatics were female biathlonsists Magdalena Forsberg from Sweden and Corinne Niogret from France. The latter met, indeed, some problems with her health, which hampered her sometimes to finish a race and then forced her to leave sport at age 31. As asthmatics, I mention a number of Norwegian biathlonsists: Egil Gjelland, Tora Berger, Ronny Hafsås, and others. After the permission to make inhalations of bronchodilators, the best Polish biathlonsist Tomasz Sikora went through the second youth. Since 2011, Russian biathlonsist Aleksei Volkov, who had EIA diagnosed several years earlier, got the right to legally use bronchial dilators”.

In the past, a number of athletes suffering from physical exercise-induced bronchial asthma attained great successes in sport, they are: swimmer Mark Spitz gained nine gold medals in Olympic

Games (OGs), seven of them in Munich; Ole Einar Bjørndalen, multiple world champion and the champion of OGs in biathlon; Bente Skari, multiple champion of OGs in ski race; Jackie Joyner-Kersey, multiple champion of OGs in athletics; Amy Van Dyken gained 6 gold medals in OGs in swimming; Paula Radcliffe, European champion in 10-km running; Jan Ullrich, winner of the cyclic criteria "Le Tour de France"; Kristine Yamaguchi, champion of OGs in figure skating; Dennis Rodman, fivefold champion of NBA; Paul Scholes, soccer player, member of the national team of England and many other outstanding athletes.

Etiology and diagnosis of EIA in athletes

Bronchial asthma, including EIA, is a chronic inflammatory disease of respiratory tracts, irrespectively severe of its course. Inflammation leads to repeated events of r le, dyspnoea, sensation of burden in chest, and cough and forms the high sensitivity of respiratory tracts to very different stimuli, which induce no reactions in healthy persons. Bronchial hyperresponsiveness can be specific and nonspecific. The latter is characterized by a high sensitivity to various stimuli of the non-allergic nature: cold air, physical load, pungent smell, stress. Thus, EIA is characterized by the presence of just a nonspecific hyperresponsiveness and arises during loads or in 5-7 min on a level of 70-75% VO_2 max and higher (Carey et al., 2010). One of the main mechanisms of its origination of the cooling of the mucosal surface of respiratory tracts appears due to the hyperventilation caused by a physical load (so-called respiratory loss of heat) (Ienna, McKenzie, 1997).

In the opinion of number researchers, the notion "physical exercise-induced asthma" implies the development of post-load bronchial spasm (in patients with atopic bronchial asthma). This opinion can be traced in materials of the Consensus "Bronchial Asthma. Global Strategy" (2008–2011) and "Bronchial Asthma in Children. Strategy of Therapy and Prophylaxis" (2006) as well as in clinic materials (National Program, 2006; Chuchalin, 2008; Baranov, Khaitov, 2011).

According to the opinion of leading specialists in this field, EIA must not be a contraindication for exercises in all kinds of sport. In other words, athletes should not be deprived of a customary physical load. But it should be dosed and controlled

in this case. Moreover, swimming is the most preferable kind of sport. However, such persons should systematically participate in prophylactic measures aimed at the prevention of the appearance of post-load bronchospasm. These measures must include the teaching of athletes, nonpharmacological methods of improvement of the functional state of respiratory system, and the use of medicinal agents (van Veldhoven et al., 2001).

The signs of EIA are sufficiently well revealed with the help of the gathering of anamnesis, instrumental studies, and data of objective examination during the implementation of functional loading tests. EIA diagnosis algorithm in athletes is sufficiently stable and includes the gathering of anamnesis (whether atopic bronchial asthma is or is not), spirometry, where the peak rate of exhalation is evaluated in the first turn, tests with inhalation of nitrogen oxide (Cowan et al., 2010) as well as the obligatory provoking tests, in particular, the direct tests with methacholine and the indirect ones with the introduction of mannitol and 4.5% NaCl solution (Schafroth T r k et al., 2014). The compulsory components of the diagnosis of EIA in athletes are also the implementation of a testing load at a laboratory and the testing under conditions of a training session. The loading tests include the execution of two tests during two training days (on a veloergometer or treadmill) with the determination of VO_2 max and the further implementation of provoking tests at 90% VO_2 max under conditions of a minimum load for at least 6-8 min, the preceding warm-up, and the inhalation of dry/cold air (the conditions of exercises and competitions of representatives of winter sport). The results of tests are positive if the peak rate of exhalation under the spirometry decreases by at least 10% of the basic values before the load. The final stage of the examination of athletes includes the bronchoscopy, which establishes the structural and morphological reconstructions of bronchial tree (Fedoseev, Trofimov, 2006).

Prophylaxis of the appearance of EIA attacks

The initial crucial component of the complex prophylaxis and efficient treatment of bronchospasm, which is caused by a physical load and is the basic symptom of EIA, is the teaching of athletes, especially young ones and their parents. It is necessary to remember that the non-pharmacological

methods of prophylaxis of EIA include the long-term warm-up, air conditioning, use of mask, limitation (before a load) of the volume of consumed food, and exclusion of products being potential allergens (Mickleborough et al., 2013). The period of intense warm-up for 30-60 min can cause the appearance of submaximal bronchial spasm followed by the refractory period from 2 to 4 h in duration (at this time interval, an athlete can quite successfully participate in sports). The series of warming-up exercises with a duration of 30 allow athletes with clinic manifestations of bronchospasm to attain a relative unresponsiveness properly to EIA and to participate in the competitive activity by provoking no attacks (Hilberg, 2007). The pharmacological component of the prophylaxis of EIA attacks is the prevention of immunosuppression (probiotic substances BioGaia, Mutaflor, M-Kurunga, Linex, Biform, Laminolact-Sporting, etc.) and the use of vitamin substances (Supradyn, Alphabet, etc.) and preparations of polyunsaturated fat acids (Epadol, Vitrumcalcium-Omega3, etc.) (Muñoz, 2004).

A sufficiently promising path in the prophylaxis and treatment of post-load bronchospasm is the use of oxidative-stress correctors and metabolics (Neuman, Nahum, 2000). Any physical load is accompanied by energy losses, and the main energy source for the muscular contraction is ATP. The medicamentous correction of metabolic breaches can lead to the formation of physical load tolerance in athletes with EIA. In particular, we may speak about L-carnitine, which is the active metabolic essentially affecting bioenergetic processes; it plays vitally crucial role in the ensuring of physiological functions of organism and the support of health. Therefore, it is considered now as a metabolic polyprotector (Olishevskii et al., 2009). Namely L-carnitine participates directly in

the catabolism of lipids by ensuring its initial stages such as the transport of long-chain fat acids in the form of complex esters from cytoplasm through external and internal mitochondrial membranes in the matrix of mitochondria. Since the energetic possibilities of organism are ones of the most essential factors limiting its physical workability, a correction of the metabolic energy-generating chain can turn out quite promising for the prophylaxis of bronchospasm under EIA (Sernova, 2003).

Of course, the main component preventing the EIA attacks is the application of bronchial dilators (inhalatory ones, in the first turn). But, in this aspect, it is difficult to separate the prophylaxis of manifestations of the given disease from its pathogenetically grounded treatment.

Treatment of EIA in athletes

The standard scheme of prophylaxis and treatment of EIA includes the application of three groups of pharmacological agents (Table). In the first turn, they are *basic*, i.e., possessing the anti-inflammatory effect, drugs including glucocorticosteroids (beclometasone, fluticasone, budesonide, flunisolide) (Al-Kazaz et al., 2012), stabilizers of mast cells (cromons), and inhibitors of leucotrienes (zafirlukast and montelukast). It is worth to note that the presence of salbutamol in urine concentration exceeding $100 \text{ ng}\cdot\text{ml}^{-1}$ or formoterol in a concentration exceeding $40 \text{ ng}\cdot\text{ml}^{-1}$ means the positive result of a test for doping.

The second group of applied agents includes *symptomatic* (mainly possessing a fast broncholytic activity) ones including the selective β_2 -agonists, cromons, and methylxanthines (theophylline). Finally, the third group is represented by the *combinations of antiinflammatory and broncholytic*

Table

Medicinal agents applied at post-load bronchospasm in athletes with EIA

Agent	Singly used	Method of application	Time (before the start of a training)
β_2 -agonists* (salbutamol, salmeterol, orciprenaline, pirbuterol, terbutalin, formoterol, fenoterol, etc.)	1-2 doses	by inhalation	5-10 min
Sodium cromoglycate (intal), sodium nedocromil	1 dose	by inhalation	10-20 min
Ditec, intal+	2 doses	by inhalation	10-20 min
M-cholinoblockers (atropine, ipratropium bromide)	2-4 doses	by inhalation	10-20 min
Theophylline	15-25 $\text{mg}\cdot\text{kg}^{-1}$	orally	1 h
β -adrenergic agents ³	various doses	orally	1 h

Notes. * – forbidden WADA substances; therefore, the therapeutic permission for their use is required, except for: 1 – salbutamol is not forbidden at the application by inhalation in the day dose of at most $1600 \mu\text{g}$, 2 – formoterol is not forbidden at the application by inhalation in the day dose of at most $54 \mu\text{g}$; 3 – are forbidden separately by kinds of sport and by training periods.

agents (seretide, composition of fluticasone propionate and salmeterol; symbicort including budesonide and formoterol) (Hodges et al., 2005).

In the treatment of EIA in athletes at the appearance of post-load bronchospasm, the great meaning is attached to pharmacological agents (Table) and, in the first turn, to selective β_2 -agonists (their synonyms are β -adrenomimetics, β_2 -adrenostimulators). They are natural or synthetic substances inducing the stimulation of β -adrenergic receptors and affecting significantly the basic functions of organism. With regard for the ability to bind with various subtypes of β -receptors, β_1 - and β_2 -agonists are distinguished. However, it should be remembered that all β_2 -agonists, including both optical D- and L-isomers, are substances forbidden in sport.

Selective β_2 -adrenomimetics are divided into two groups by the action duration. The agents with short-term action include fenoterol, salbutamol, terbutalin, hexoprenalin, clenbuterol; the latter is referred to the substances forbidden in sport (Class S1. Anabolic agents, subclass 2. Other anabolic agents) for any form of its introduction into organism. The agents with long-term action include salmeterol, formoterol, and indacaterol. As side-effect at the use of β_2 -adrenomimetics by inhalation, tachycardia, tremor, sometimes hyperglycemia, excitation of the central nervous system, and a decrease in the arterial pressure are observed most frequently. At the parenteral application, all these phenomena are pronounced more clearly.

Most frequently, athletes with EIA use salbutamol, formoterol, and fenoterol by inhalation (namely this form of introduction is allowed) (Prohibited List, 2016). Thus, if the presence of EIA is confirmed, athlete should get a certain dose of drugs referred frequently to the forbidden ones. Therefore, athlete must obtain a therapeutic use exemption (TUE) in order to use them.

The implementation of the basic therapy accepted for bronchial asthma is accompanied by a decrease of the reaction of bronchi to a physical load. In this aspect, it is worth to note the efficient action of β -adrenergic drugs and sodium cromoglycate (intal), which inhibits the degranulation of mast cells in lungs and hampers, release biologically active substances-mediators from them; mediators such as, in the first turn, bradykinin, histamine, and leucotrienes that favour the development of bronchospasm. Sodium

cromoglycate and sodium nedocromil prevent post-load bronchial spasm as well as the majority of bronchial asthma attacks, including EIA, which are induced by nonpharmacological provocateurs (Kivity et al., 1999).

Rapidly acting β_2 -agonists ensure the protection for 80–95% athletes with EIA with slight side effects, and M-cholinoblockers do for 50–70%. For many years, these agents were considered as the first-line therapy. It was determined that, under a physical load, salmeterol and formoterol render the protective action for 9–12 h, and salbutamol do for 0.5–2.5 h. It should be noted that the bronchoprotective effect under a physical load decreases at the long-term application of β_2 -agonists and the introduction of methacholine. Bronchoconstriction induced by a physical load is also affected, in a dose-dependent manner, by such inhalation corticosteroids as budesonide, flixotide, and inhacort (Koh et al., 2007). Fortunately, the pharmacological agents on the basis of glucocorticosteroids introduced by inhalation do not yet enter the Prohibited list (2016).

The highest efficiency concerning the prophylaxis and the treatment of EIA is revealed by modifiers of the synthesis of leucotrienes. The first work on their role at EIA were published 20 years ago (Finnerty et al., 1992). At the present time, three groups of agents able to affect the synthesis of leucotrienes are available: inhibitors of the activity of 5-lipoxygenase, inhibitors of a 5-lipoxygenase-activating protein, and antagonists of leucotriene receptors. We note the widest clinic use of the antagonists (modifiers) of leucotriene receptors (zafirlukast, montelukast, pranlukast) and an inhibitor of the biosynthesis of leucotrienes (zileuton). In the process of implementation of the antileucotrienic therapy, the fast clinic improvement is observed in athletes with EIA of any degree of severity against the background of the simultaneous normalization of the functional parameters of external respiration (Carver Jr., 2009).

The antileucotrienic drugs (zafirlukast and montelukast) prevent EIA attacks by suppressing the synthesis of sulfopeptide leucotrienes. The intake of antileucotrienic drugs decreases the need of patients in β_2 -agonists. In addition, it is known that the antileucotrienic drugs are more efficient under EIA than cromons (for the latter, the bronchoprotective effect at a provocative test by a physical load lasts 2 h) or β_2 -agonists forbidden in sport (Ali, 2011).

At present, the modes of prescription of the modifiers of leucotrienes as a monotherapy of EIA are intensively discussed. Since these drugs, as distinct from β_2 -agonists with long-term action (salmeterol, formoterol), possess antiinflammatory properties, their application in the case of a light course of EIA seems to be promising (Carver Jr., 2009). It is of especial importance for the treatment of young athletes with post-load bronchial spasm, when the immediate prescription of hormonal drugs is not recommended. The peroral reception of the modifiers of leucotrienes favours the attainment of a high level compliance. As compared with corticosteroids, these drugs have such advantages as the security and a flexible mode of their use (one or two times for a day) (Kubota et al., 2000). For young athletes (older than 6 years) with EIA, only montelukast (Singular, "Merck") in the form of a bubble gum by 4 mg and zafirlukast (Accolate, "Astra Zeneca") are allowed. It was found that the application of these drugs allows one to decrease the intensity of symptoms of EIA and to improve the tolerance of a physical load at the use of only a single dose (Milgrom, Taussig, 2009).

However, it should be remembered that these highly specific efficient drugs decrease intensively the manifestations of bronchospasm only in 65–67% athletes. The degree of efficiency of an antileucotrienic drug for an athlete with EIA can be determined in 2-3 weeks from the start of therapy, though the majority of asthmatics demonstrate the reliable increase in the peak rate of exhalation already in 3-4 days after the reception of a drug. The mechanism of resistance to the modifiers of leucotrienes has not been yet finally established (O'Byrne, 2000; Carlsen et al., 2008).

Under bronchospasm related to physical loads, the antagonists of calcium (nifedipine, nitrendipine, nimodipine, amlodipine, lacidipine, felodipine, nicardipine, isradipine, lercanidipine; diltiazem, clentiazem, etc.), anticholinergic drugs of the type of ipratropium bromide, and α -adrenoblockers of the type of prazosin can be used as well.

The arresting of EIA attacks was made also with the help of the inhalations of diuretics. The encouraging results concerning the prevention of bronchospasm were obtained by the inhalation of furosemide (Milgrom, Taussig, 2009). It turns out that furosemide sufficiently well protects bronchial tree from the provocative action of a physical load,

inhalations of distilled water, and antigens. The action of furosemide is explained that it causes the increase in the local synthesis of prostaglandin E_2 possessing the vassal and bronchial dilatation effects, rather than by its influence on the K^+ - Na^+ cellular mechanism. In this case, it is worth to emphasize that the use of diuretics (etacrynic acid, furosemide, indapamide, spironolactone, chlorothiazide, etc.) is forbidden in the period of sports and outside it. Moreover, the detection of the use of β_2 -agonists (e.g., salbutamol, cathine, formoterol) in any concentration together with diuretics will be considered as the positive result of the test for prohibited substances, if athlete has no permission for the therapeutic use of diuretics (e.g., at a disfunction of kidneys, hypertension, etc.) (Carlsen et al., 2008; Prohibited List, 2016).

To a definite extent, post-load bronchial spasm is facilitated by antihistamine drugs (azelastine, loratadine, desloratadine, chlorpheniramine, cetirizine, ketotifen, dexofenadine, etc.), which are not fortunately referred to the prohibited ones. Finally, as the recent developments in the therapeutic strategy at EIA, we mention the recombinant humanized monoclonal IgG1kappa-antibodies (e.g., omalizumab), which bind selectively with IgE of a patient by favouring the efficient prophylaxis and treatment of bronchospasm at EIA (Bray et al., 2012; Vichyanond, 2011).

Conclusions

The presence of physical exercise-induced asthma is not the absolute contraindication to sport exercises and gives possibility to attain certain successes in sport, if the therapeutic permission is available with the medicamentous control over its manifestations with regard for the WADA principles concerning the use of prohibited substances.

To diagnose "physical exercise-induced asthma" in athletes, it is necessary to clearly keep the algorithm of examination, including the implementation of loading tests under real conditions of exercises.

Prophylaxis and therapy of the disease should include non-medicamentous and medicamentous agents.

If the diagnosis "physical exercise-induced asthma" is established, the corresponding sport federation should take care of the receipt of a therapeutic permission of the use of agents forbidden in sport practice.

Sport doctors and allergists realizing the treatment of athletes with EIA must try to use as least as possible prohibited substances by preferring the modern pharmacological agents in the prophylaxis and the arresting of post-load bronchial spasm. If such therapy is not sufficient, the attending physicians must supplement the complex treatment by β_2 -agonists by orienting on their allowed dose or, if it is not sufficient, on higher doses at the appropriate therapeutic permission.

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SPORTININKŲ BRONCHINĖ ASTMA DĖL FIZINĖS ĮTAMPOS: NEATSAKYTI KLAUSIMAI,
PROFILAKTIKOS IR GYDYMO GALIMYBĖS (APŽVALGA)

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SANTRAUKA

Sportininkų bronchinė astma dėl fizinės įtampos yra liga, kuri priverčia sportininką nutraukti treniruotes ir varžybas. Tačiau laiku ir tinkamai besigydantys sportininkai gali dalyvauti varžybose ir pasiekti puikių rezultatų. Bronchinės astmos dėl fizinės įtampos diagnozės algoritmas, be standartinio medicininio ištyrimo, numato testavimą, kai natūraliai vykstančio treniruotės proceso metu modeliuojami krūviai siekiant įvertinti maksimalų iškvėpimo greitį. Sportininkų, sergančių šia liga, bronchokonstrikcijos priepuolių profilaktika atliekant fizinius krūvius turi būti siejama su mokėjimu laikytis dietos, būtina intensyvaus krūvio pramankšta, farmakologinių preparatų, turinčių tropinį, imunomoduliuojantį ir energinį

poveikį, vartojimu. Bronchinės astmos dėl sportininkų fizinės įtampos gydymo taktika turi atsižvelgti į tai, kad didžioji dalis bronchodiliatorių preparatų sporte įtraukti į draudžiamų vartoti medžiagų sąrašą. Pastaruoju metu egzistuoja kryptingi šios ligos profilaktikos ir gydymo metodai vartojant nedraudžiamus gydomuosius, astmos priepuolius slopinančiuosius (Zafirlukast, Montelukast) preparatus. Jie yra leistini vartoti tiek jauniems, tiek didelio meistriškumo sportininkams ir duoda didelį terapinį efektą, esant nedideliems šalutinio poveikio požymiams.

Raktažodžiai: bronchinė astma dėl fizinės įtampos, sportas, profilaktika, gydymas, bronchų kraujagysles plečiantys ir siaurinantys preparatai.

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