Original Article

Effort-induced bronchospasm in athletes: modern views on pathogenesis and diagnosis in high-school teenagers

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ABSTRACT

Effort-induced bronchospasm (EIB) is a common bronchial asthma manifestation in response to physical activity and occurs in the absolute majority of this patient group. It is widespread among apparently healthy teenagers intensively engaged in sports, which is due to several factors including climate patterns, training conditions, and high physical activity intensity. The special relevance of BFN for adolescents who are actively engaged in sports is due to the high prevalence. So, if the frequency of BFN in the general population of persons of this age group does not exceed 5-10%, then among adolescents intensively and regularly engaged in sports, this indicator reaches 25%. Clinical manifestations of BFN are associated with impaired respiratory function, which develops in response to increased physical activity. In BPH, the decrease in external respiratory function is based on a rapidly developing transient narrowing of the lumen of the respiratory tract, provoked by physical exertion. With BFN, there is a more pronounced decrease in FEV1, which reaches 10-15% of the initial value. This condition is accompanied by a violation of the external respiratory function during the training process and leads to a deterioration in sports performance, and also provokes the development and progression of the respiratory system diseases. Currently, there is no definitive understanding of all pathogenetic aspects of BFN. The methods used for the diagnosis of BFN do not always allow to identify this condition with high confidence. The paper presents a literature review about various aspects of EIB in high-school teenagers active in sports.

Keywords: Effort-induced bronchospasm, Bronchial asthma, Athletes, High-school teenagers

Introduction

Effort-induced bronchospasm (EIB) is a common pathological condition among high-school teenagers (15-17 years old) suffering from bronchial asthma, which is observed in 90% of patients with the disease. EIB clinical signs are associated with an impaired respiratory function that develops in response to increased physical activity. Moreover, EIB is diagnosed not only among patients with bronchial asthma but quite often complicates the course of other respiratory diseases, including chronic obstructive pulmonary disease (COPD), allergic rhinitis, etc. [1]. An important feature of EIB is that this condition is observed not only in the background of chronic abnormal respiratory changes but is also diagnosed in apparently healthy people [2].

At the heart of the respiratory function depression in EIB is the rapidly developing transient diminution of respiratory passages, provoked by physical activity. Thus, under physiological conditions, forced expiratory volume per 1 second (FEV1) on the background of intensive physical activity is reduced by 5% roughly. With EIB, a significantly more pronounced decrease in

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FEV1 is observed, usually reaching 10-15% of the initial value [3].

EIB development is of particular relevance for teenagers actively involved in sports. Thus, if the EIB prevalence rate in the general population of people of this age group does not exceed 5-10%, then among teenagers who are actively and regularly do sports, this figure reaches 25%. Contemporary authors attribute the higher EIB incidence rate among athlete teenagers to a number of predisposing factors, these include both the fact of super-intense physical activity and closer medical supervision. The latter factor suggests more intensive supervision recording all EIB episodes, as well as episode challenges during examination aimed to detect respiratory and cardiovascular system tolerance to increased physical activity [4].

A contemporary view on EIB in athlete teenagers makes it possible to rather clearly differentiate this disease from bronchial asthma [5]. EIB development is directly associated with super-intensive physical activity, while the key role in bronchial asthma pathogenesis is played by the chronic autoimmune inflammatory process, the clinical signs of which may be caused by other trigger factors. However, severe physical activity can be a predisposing factor to the inflammatory process occurrence and progressing in the respiratory tract formation, accompanied by leukocyte-infiltrated mucous membrane, cysteinyl leukotriene production, and other pathophysiological processes that are characteristic of the bronchial asthma course. Under such conditions, it becomes quite difficult to differentiate EIB from bronchial asthma due to the lack of clear diagnostic criteria. This circumstance causes significant difficulties in interpreting the research results devoted to the study of EIB and bronchial asthma course peculiarities in teenagers doing actively sports [6, 7].

However, regardless of bronchial asthma, EIB prevalence among athlete teenagers is extremely high, ranging from 11 to 50% according to various studies. EIB development on the background of physical activity significantly lowers sports results. At the same time, most researchers point out that occurring complaints of difficulty of respiration are not a reliable sign of EIB disease, the diagnosis of which requires an objective respiration function study [8-10]. This aspect is extremely important for athlete teenager taking part in high-level competitions since in order to be able to administer drugs that reduce the likelihood of bronchospasm development, it is necessary to confirm the "bronchial asthma" diagnosis based on the detected significant depression in respiration, primarily FEV1, when conducting bronchoprotection examination.

A significant factor in EIB and bronchial asthma development is systematic intensive training in cold climate conditions. Thus, according to a number of researchers, 23% of EIB cases are professional athletes doing winter sports. At the same time, this condition is diagnosed more often in women (26%) cases, compared to men (18%) [11]. The highest EIB prevalence rate is found in long-distance skiing athletes [6, 12]. In general, the results of these studies can be extrapolated to athlete teenagers belonging to the older age group, given the fact that their EIB development pattern is the same as that of adult athletes.

Thus, it can be summed up that EIB is a major problem not only for modern sports medicine but also for pediatrics. At the same time, the greatest relevance is characteristic of teenagers doing winter sports. EIB prevalence among athlete teenagers, especially those engaged in the sport of setting records, planning to devote themselves to professional sports, necessitates further research on a comprehensive study of this problem.

Materials and Methods

When writing this article, the following methods were used: general scientific (dialectical, analysis and synthesis of literature data available, comparisons and analogies, annotating, inspecting, and reviewing data obtained from modern scientific sources) and special (systematic, comparative analysis, etc.) methods.

Results and Discussion

Peculiarities of effort-induced bronchospasm pathogenesis in high-school teenagers

In recent years, the results of a number of studies examining pathogenetic EIB mechanisms have been published. Despite this, there is still no consensus on the specific pathophysiological causes that trigger this condition. Most authors adhere to one of the two hypotheses [13]. The first one is the thermal hypothesis, which is based on the role of heat exchange in respiratory passages. Researchers that adhere to this hypothesis indicate that with intense physical activity there is an increase in bronchial mucous membrane cooling due to an increase in the volumetric ventilation rate. This process is the reason for mucous membrane compensatory heating, associated with vasodilation and increased wall permeability, which leads to swelling and airway diminution.

The second hypothesis presented in modern literature is called osmotic and suggests that the key point of EIB pathogenesis is the intense evaporation of fluid from the surface of the airway mucous membrane. At the same time, liquid remaining on the surface becomes hyperosmolar, which is accompanied by water migration from surrounding cells to the intercellular space leading to their destruction. These processes lead to mast cell degranulation with the release of inflammatory mediators, the effect of which on bronchi smooth muscles causes their contraction, the clinical signs of which is EIB development [14].

Most likely, these theories describe two simultaneous processes, both of which play a certain role in the EIB pathogenesis [13].

The importance of inflammatory mediators in pathophysiological mechanism formation in EIB development is described in a number of modern studies [15, 16]. For a long time, histamine was considered the key mediator responsible for pathological process formation. However, contemporary authors point to the leading role of leukotrienes (LT) and prostaglandins (PG), which are now considered the key pathogenetic factors triggering both bronchial asthma and EIB. These mediators determine clinical pronouncement and duration of pathological state course. Pathophysiological processes peculiar to EIB, such as bronchial remodeling, bronchospasm development, increased vascular wall permeability, eosinophil migration to the inflammation area, smooth muscle tissue proliferation, and hypersecretion are triggered by cysteinyl LT [15, 17]. The greatest biological activity among these inflammatory mediators is common to LT C4, which is metabolized in LT D4, and then into the E4 form, which is excreted in the urine. Rapid LT E4 excretion with normal kidney function causes an increase in its serum level only with an increase in lung production [18]. The results of modern studies demonstrate an increase in the excreted with urinary prostaglandin metabolite D2 and LT E4 after intensive physical activity. People suffering from EIB were diagnosed with a significant increase in the concentration of cysteinyl LT, histamine, and tryptase in sputum when taking physical activity [19]. Decreased level of inflammatory mediators in sputum has been found to be associated with the administration of drugs such as montelukast and loratadine [16].

As a result of some studies, it was found that people with EIB who regularly have intensive physical activity show a significant increase in excreted in urine prostaglandin F2 and LT E4. At the same time, straight after physical activity is taken, an increase in the LT V4 and LT C4 mediator concentration in the blood is observed. It has also been found that intensive physical activity is the most important factor to initiate cysteinyl LT production due to activated gene expression responsible for the 5-lipoxygenase eicosatetraenoic acid transformation pathway [19, 20].

In the current literature, there is conflicting evidence regarding the role of nitric oxide (NO) in the formation of pathophysiological mechanisms for EIB development. Thus, when comparing the group of patients suffering from bronchial asthma and EIB with the group of healthy people, it was found that NO concentration is significantly higher for the first group. At the same time, NO level correlation with the increase of bronchial vessel wall permeability and clinical disease severity is noted [21-23].

It was found that there is an inverse correlation between the NO concentration and the FEV1 index. It is now considered proven that bronchial asthma associated with EIB is accompanied by an increase in NO production associated with airway obstruction severity. At the same time, reduced NO production is associated with retrograded EIB clinical signs severity [24]. On the other hand, some literature sources present data showing that there is no identified association between the EIB severity and NO production [25].

One of the most significant aspects of studying the peculiarities of bronchial asthma and EIB course is the analysis of sputum to detect the concentration of various biologically active agents and to study cellular composition, which are significant criteria to assess the course and severity of the inflammatory process occurring in the respiratory tract. In a number of clinical studies, it was found that there is a significantly higher number of eosinophils in sputum in patients with bronchial asthma and EIB compared to healthy people, as well as a significant increase in the eosinophilic peroxidase level [26, 27]. A distinct correlation has been demonstrated between bronchial inflammatory process severity and the disease course severity. At the same time, athletes suffering from EIB are characterized by more pronounced eosinophilia than those who do not have bronchospasm symptoms. Thus, the indicator for group 1 is 7.6%, while it is 0.7% for group 2 [27].

Signs of local inflammatory response were revealed in the sputum analysis of the examined people intensively engaged in various sports: skiing, hockey, swimming [28-30]. These signs involved a significant number of lymphocytes, eosinophils, and neutrophils in sputum. At the same time, the authors noted the correlation between the severity of EIB and inflammatory process clinical signs. As a result of morphological studies of bronchial biopsy sample taken from young people intensively engaged in skiing race, a significant intensity of neutrophilic infiltration was revealed. Importantly, no similar inflammatory changes were observed when examining material obtained from patients with bronchial asthma [28, 30]. The researchers pointed to bronchial tissues significantly lower infiltrated with eosinophils, macrophages, and mast cells. Thus, certain signs peculiar to the bronchial mucous membrane inflammatory process in athletes engaged in winter sports were revealed. Similar conclusions were reached by the authors of the research studying the level of macrophages and white blood cells in the material obtained in bronchoalveolar lavage (BAL), which resulted in a significant increase in the number of these cells in healthy athletes after intensive training under low-temperature conditions [31].

During the prospective clinical study, an advanced local inflammatory process in intensively training swimmers was revealed on the background of initially moderately infiltrated bronchial mucous membrane with eosinophils and lymphocytes [32]. It was noted that in the group of athletes who stopped taking intensive physical activity, there was a regression in respiratory tract inflammatory changes and clinical signs of EIB and bronchial asthma. The authors concluded that there is a clear correlation between taking intensive physical activity and bronchial inflammatory event aggravation, as well as with the increase in the EIB symptom severity, the disappearance of which is associated with the cessation of regular training loads. Similar inflammatory changes in the respiratory passages were revealed when examining long-distance runners [30]. A positive correlation was also detected between the exhaled NO index immediately after doing an exercise and the degree of bronchial inflammatory infiltration [24, 33].

An independent pathogenetic factor in bronchial asthma and EIB development in athletes is the atopy and its severity. It was found that the atopy event compared to the lack of it increases the risk of EIB by 25 times in weightlifters and sprinters, by 42 times in long-distance runners, by 97 times in swimmers [34, 35]. It has also been proven that an important pathophysiological mechanism for EIB development in athletes is a significant increase in minute ventilation in the background of intensive physical activity. This indicator increases from 8-9 min^{-1}. At rest up to 150-180 min^{-1} with increased physical activity, which contributes to an increased pollutant and aeroallergen exposure dose in the respiratory tract.

An important aspect of the EIB pathogenesis is the factors that cause a change in the immune system when exposed to intense physical activities that are stressful for the athlete's body. It is proved that on the background of taking super-intensive physical activity, athletes develop a transient immunodeficiency state, associated with a high risk of airway infectious-inflammatory process development. According to contemporary authors, the reason for the significant prevalence rate of acute respiratory viral infections (ARVI) among athletes, as well as allergic diseases, is a change in the balance of pro- and anti-inflammatory factors, inflammatory mediators being predominant [36, 37].

Recently, significant attention has been drawn to research aimed to identify mechanisms that contribute to the interaction between the neuroendocrine and immune systems when taking intensive physical activity. It was established that physical activity potentiates pituitary-hypothalamic and sympathoadrenal system activation. This process is accompanied by an increase in corticotropic hormone production, which has a control effect on catecholamine and glucocorticosteroid secretion, which have a modeling effect on immune responses [37, 38]. In addition, stress induced by intensive training leads to cytokine release from immunocompetent cells. Cytokines, in turn, by influencing hypothalamus function, have a control effect on glucocorticosteroid [39]. It has been proven that some interleukins (IL), such as IL-1 and IL-6, have a potentiating effect on pituitary-hypothalamic and sympathoadrenal system activation, as well as corticotropic hormone production. Similar properties were found in α tumor necrosis factor (TNF-α). Currently, there is confirmed evidence that intensive physical activity is an important factor that has a fairly significant effect on not only pro-inflammatory (IL-12, TNF-α, interferon-γ), but anti-inflammatory (IL-10) mediator production as well [40]. A certain role of endogenous catecholamines in cytokine release control has been established. On the background of physical activity, these hormonal factors actively enter the systemic bloodstream and by affecting β2-adrenoreceptors increase IL-10 production with no immediate effect on immunocompetent cells. Physical activity also stimulates increased adrenal glucocorticosteroid secretion, which potentiate interleukins release by type 2 T-helpers. Thus, the described mechanisms contribute to disrupting the balance between anti- and pro-inflammatory mediators. Increased physical activity causes systemic endocrine and immune process activation promoting inflammatory process activation [38, 41].

It should be noted that most modern authors point to the lack of significant differences between the EIB pathogenesis in adult athletes and high-school teenagers actively involved in sports [9].

Effort-induced bronchospasm diagnosis

A crucial aspect of effort-induced EIB and asthma diagnosis in high-school athlete teenagers is the need for its distinct standardization. This is due to the fact that some of the drugs to treat asthma are included in the list of drugs prohibited by the international anti-doping committee. On the other hand, it is obvious that the selected diagnostic criteria are adequate to solve the task to select the most effective drug treatment regimens regulated by modern clinical guidelines. In addition, an important aspect affecting definition of EIB diagnostic methods and criteria in teenagers is the need to differentiate athletes into groups having EIB, those with anamnesis record and those suffering from other respiratory diseases.

The diagnostic approaches to detect and verify EIB and bronchial asthma in teenagers actively involved in sports are based on identification of anamnestic data and clinical signs indicating bronchial obstruction on the background of intensive training, as well as the respiration function study and provocative testing [6, 39].

Currently, various types of special questionnaires for the people examined are used to identify anamnestic and clinical signs of bronchial obstruction, establish their correlation with physical activity and determine other parameters that enable identifying EIB. As a rule, an important factor limiting the diagnostic value of the respiratory function study is the lack of deviations in its diagnosis in athlete teenagers suffering from EIB and/or bronchial asthma. Therefore, in order to reliably make or rule out a diagnosis, provocative testing is usually required [9].

Tests used to detect EIB and bronchial asthma in athlete teenagers are divided into direct and indirect [6]. Direct provocative tests include eucapnic hyperventilation, indirect tests include methacholine testing. Direct tests have more sensitivity but significantly less specificity. In turn, the indirect (methacholine) test, on the contrary, is characterized by considerable specificity against the background of relatively low sensitivity [42]. The criterion to determine bronchial hyperresponsiveness by eucapnic hyperventilation testing (single-step or multi-step) is a decrease in FEV1 by 10 or more percentage points [43]. One of the most common provocative tests in athletes, including older teenagers, that Olympic Committee is based on the results of which, is the standard methacholine testing. The bronchial hyperresponsiveness criterion in methacholine testing is the provocative methacholine concentration value, accompanied by a decrease in FEV1 by 20%, less than 13.2 mg/ml, which indicates moderate bronchial asthma in athletes taking topical hormonal drugs. A value of less than 2 mg/ml corresponds to severe asthma. At the same time, the methacholine test has a significant drawback, particularly insufficient sensitivity of the method in the least pronounced subclinical disease forms [42].

An important method to identify EIB in athlete teenagers is the exercise test. It was established that bronchospasm signs appear in 80% of teenagers suffering from bronchial asthma on the background of physical activity. Therefore, physical activity is widely used as a provoking factor to diagnose EIB. This is due to the fact that it is impossible to claim no EIB detected reliably based on the methacholine test results. Among other things, the reason is the fact that only 5% of high-school athlete teenagers engaged in athletic sports show signs of bronchial asthma, while 30% of them show EIB symptoms. Given that under low-temperature conditions, the risk of EIB development significantly increases, it is advisable to conduct a physical exercise test regarding the specific sport that the examined person is engaged in. Thus, the test must be done under conditions close to the training and/or competitive process. One of the important conditions for test result reliability is to achieve hyperventilation with FEV1 values exceeding normal values by 15-22 times. It is also essential to maintain humidity at less than 50% [38]. The most common options to carry out a physical exercise test are treadmill, running, or cycling ergometer. The use of cycling ergometry is most widespread since its use allows for more accurate physical activity dosing. Physical activity intensity is selected based on maximum heart rate the specific value of which is calculated by a formula: MHRmax =220-age (years) [42, 44]. Another method applied is to determine the oxygen consumption level [45].

The standard exercise test protocol involves increasing exercise intensity performed in the 1st minute to 60% of the maximum HR, to 75% in the 2nd minute, and to 90% in the 3rd minute. Subsequently, the reached load intensity is maintained during 4-6 minutes [46]. Respiration function is examined immediately after the exercise is finished and 20 minutes later. In case the examined person does not take systemic or inhalation hormonal drugs, a diagnostically significant sign to detect EIB is a 15% or more FEV1 decrease compared to the initial level. When conducting the test, the FEV1 decrease is differentiated by light, medium, and heavy, which implies a value decrease by 15-24%, 25-49%, and ≥50% of the initial value, respectively. As a rule, athlete teenagers suffering from EIB are characterized by an FEV1 decrease within 10 minutes after the end of the physical activity effect. At the same time, the indicator recovery to the initial value is observed within 30 minutes after the end of the test. Most authors point out that in order to obtain the most reliable exercise test result before it starts it is required to cancel all drug intake that reduces bronchial hyperresponsiveness for a period corresponding to the duration of action of these drugs [46].

Conclusion

Thus, EIB is a fairly common pathological condition not only among high-school children suffering from bronchial asthma or other respiratory diseases but also among healthy teenagers actively involved in sports. Among athlete teenagers engaged in athletic sports, the EIB prevalence rate reaches 30%. At the same time, this condition is associated with a violation of respiration function in the course of the training process and leads not only to a deterioration in sports, but can also trigger respiratory disease development and progression. Currently, there is no complete understanding of all pathogenetic aspects of EIB development. The methods used to diagnose EIB do not always enable highly reliable state detecting. The presented literature review demonstrates the high relevance of further pathogenesis study and the development of new methods to diagnose EIB in high-school teenagers, increasing examination result validity, which will allow for timely and effective treatment.

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