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Exercise intolerance and exercise-induced bronchoconstriction in children

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1. ABSTRACT

Respiratory symptoms at rest or during exercise may restrain the physical capabilities required for normal motor and psychosocial development in children. The most frequent cause of exercise intolerance, apart from poor physical fitness, is exercise-induced bronchoconstriction (EIB), which may occur in some healthy children and in children with asthma. It is proposed that hyperventilation during exercise is associated with drying and cooling of airways, which can trigger a proinflammatory response. Several tests are used to confirm EIB, and the exercise-challenge test is the most common. Some nonpharmacologic therapies may induce airway refractoriness; warm-up exercise can result in the attenuation of EIB in more than half of the people with EIB. Prophylactic intermittent treatment with short-acting bronchodilators is the most commonly used treatment, but the conventional pharmacologic therapy for patients with uncontrolled asthma is the regular use of inhaled corticosteroids, with or without long-acting beta-agonists and montelukast. Therapy should result in optimal control of exercise-induced symptoms during habitual physical activity and also allow participation in sports activity in athletes.

2. INTRODUCTION

Physical activity is necessary for normal growth and development in childhood. It is well known that the children who are not sufficiently physically active because of various chronic diseases may have numerous physical, psychological and psychosocial limitations. Respiratory symptoms during exercise may limit children's ability to be physically active. The most frequent cause of exercise intolerance, apart from poor physical fitness, is exercise-induced bronchoconstriction (EIB), which is mostly associated with wheezing during exercise. The prevalence of self-reported exercise-induced respiratory events varies among the general adolescent population between 14-19.2 percent (1, 2). In athletes without known asthma, the prevalence is even higher, up to 30 percent (3). These events occur more frequently in athletes practicing sports with high minute ventilation in a cold environment (e.g., cross-country skiing) or with high exposure to toxins (e.g., ice hockey). The results of two large cohort studies showed that in children younger than five years of age, exercise-induced wheezing and cold dry air hyperpnea were the strongest predictors of asthma later in life (4, 5). Several other disorders, such as chronic cardiac or lung diseases, congenital malformations of

airways, exercise-induced hyperventilation or exercise-induced laryngeal obstruction, may result in respiratory problems during exercise. The most frequent disorder among these is chronic lung disease of prematurity (CLD) (6). Joshi *et al* (7) showed that school-age children who experienced CLD in infancy had a significantly higher incidence of EIB that responded significantly to bronchodilators.

The aim of this article is to provide an overview of the physiological response to exercise with special consideration for the etiology, diagnosis and treatment of exercise-induced wheezing.

3. PHYSIOLOGICAL RESPONSE TO EXERCISE

In healthy children, energy consumption is mainly determined by the degree of physical activity. Patients who are unable to perform certain physical activities have exercise intolerance. The exercise capacity is directly related to the capacity of the respiratory and cardiovascular systems to deliver oxygen to muscles and to the ability of muscles to take oxygen from the blood and use it in mitochondrial oxidative processes (8). The energy, stored as glycogen and fat depots, can be used during the processes of cellular metabolism.

The process of muscular contractions is associated with energy consumption through the hydrolysis of energy-rich molecules of adenosine triphosphate (ATP). ATP hydrolysis leads to the release of a phosphate molecule and energy, which is necessary for muscle activity. Intracellular ATP reserves are only sufficient for a few muscle contractions, so the most important source of new ATP molecules is the process of oxidative phosphorylation. During exercise, oxygen is extracted from the arterial blood to a greater extent, which results in a reduction of the oxygen content in venous blood. In addition, there is an increase in minute ventilation (MV) and lung perfusion, which results in an increase in the oxygen content in the pulmonary veins. The adaptation of the cardiovascular system to exercise is based on the increase in cardiac output, the redistribution of circulation through vasodilatation of the arterioles in the involved muscles and the elevation of arterial blood pressure.

A progressive increase in muscle load finally leads to muscle fatigue, which is characterized by exhaustion of aerobic metabolism. Additional energy is obtained from anaerobic glycolysis, which is less efficient. When exercising muscles are not capable of meeting the increased metabolic needs, muscular fatigue develops, which is followed by anaerobic metabolism and lactic acidosis. The respiratory system is capable of compensating these conditions through a further increase in MV and increased elimination of carbon dioxide (VCO_2) For mild and moderate levels of activity, the increased $\dot{M}V$ is a result of an initial increase in the tidal volume (V_T), but at a higher level of activity, it is also followed by an increase in respiratory frequency. The level of oxygen consumption (VO_2) at which there is a net increase in the lactate concentration in serum is called the anaerobic threshold (AT). The ratio of VO_2 and VCO_2 is called the respiratory exchange ratio (RER). An RER value greater than 1 is a true sign of the exhaustion of aerobic metabolism (8, 9).

In most healthy subjects, exercise is terminated with a preserved respiratory reserve, because in these subjects, exercise intolerance is mostly caused by muscle fatigue. In some patients with obstructive lung diseases, these compensatory mechanisms are inefficient, which may lead to a reduced oxygen content in arterial blood with decreased hemoglobin oxygen saturation (SpO_2) and finally, to the demonstrated metabolic acidosis. Rarely, highly trained athletes may have a ventilatory limitation on the maximal effort because of the exhaustion of the normal ventilatory reserve as a result of ideal aerobic metabolism in exercising muscles.

In subjects with respiratory diseases, regardless of the etiology, two major factors describe the pathophysiology of exercise intolerance – decreased ventilatory capacity and increased ventilatory requirements (8). Decreased ventilatory capacity in children with obstructive lung diseases is mostly caused by increased pulmonary resistance, which leads to progressive airway obstruction. Increased ventilatory requirements are caused by a mismatch between ventilation and perfusion. In patients with severe airway obstruction, $PaCO_2$ often increases during exercise because the increased work of breathing worsens metabolic acidosis. Ventilatory limitation and dyspnea, as well as muscle fatigue during a progressive effort, lead to exercise intolerance in these patients.

Pain in the chest, arm or neck, which is a common symptom of myocardial ischemia, or claudication, which occurs because of an inadequate oxygen supply of the muscles of the lower exercising extremities, occur infrequently in children.

4. REASONS FOR EXERCISE INTOLERANCE

In a number of patients with exercise intolerance, typical symptoms of the disease occur during physical effort. Common diagnostic procedures are necessary to confirm diagnosis (i.e., echocardiography or spirometry). Cardiopulmonary exercise testing (CPET) offers the best insight into pathophysiological mechanisms and interactions that could explain exercise-induced symptoms, such as wheezing, chest tightness, difficult breathing or dyspnea (when several mechanisms are possible).

Testing exercise tolerance in healthy subjects and patients with respiratory, cardiovascular, skeletal muscle, and metabolic disorders is complicated. The complex method is based on the principle that the insufficiency of a complex organic system usually occurs in its exposure to stress, which can be tested in controlled laboratory conditions. Exercise intolerance occurs when a person is unable to sufficiently maintain the degree of effort that is necessary to accomplish the previously set goal (10, 11). During the gradual increase in the physical load on the ergo-bike or treadmill, the lung ventilation, gas content in exhaled air, SpO_2, heart rate, electrocardiogram (ECG) and blood pressure values are measured and analyzed.

4.1. Disruption of oxygen transport

Oxygen transport to working muscles depends on cardiac output (CO), tissue perfusion and the oxygen content of arterial blood. If one or more of these factors are insufficient, there will be a reduction in the concentration of oxygen in muscles.

Cardiac output is a function of preload, afterload and myocardial contractility. In patients with heart failure, severe cardiac arrhythmia and severe arterial or pulmonary hypertension, CO may be decreased. An increase in metabolic need in such patient leads to premature exhaustion of compensatory mechanisms, low VO_2 on maximum load (W_{max}), and a very rapid increase in RER, and it manifests as hypoxemia and acidosis.

Patients with severe anemia have low arterial oxygen content due to low hemoglobin levels. These patients very often have malaise and exercise intolerance, which can be improved by treatment.

4.2. Disorders of gas exchange in the lungs

Widening or fibrosis of the pulmonary interstitial space, which occurs in interstitial lung diseases or in pulmonary edema, results in impaired diffusion of respiratory gases, mostly oxygen, through the alveolocapillary membrane. In severe emphysema, there is also a reduction in the total surface of the respiratory membrane, which may also lead to diffusion problems. This problem is aggravated by increased ventilation of improperly perfused lung units (dead space ventilation). The best insight into the percentage of blood that leaves pulmonary circulation without being oxygenated (amount of pulmonary shunt) can be obtained by calculating the alveolar-arterial gradient for oxygen ($AaDO_2$).

4.3. Disorders of ventilation

An increase in the concentration of CO_2 in arterial blood ($PaCO_2$), acidosis and a reduced concentration of oxygen (PaO_2) are the stimuli for an increase in ventilation during exercise. The maintenance of the respiratory gas concentrations in arterial blood within normal ranges is influenced by the functional ability of the respiratory system. This capacity can be estimated by maximal voluntary ventilation (MVV), which represents the maximum amount of air that can be exhaled during forced breathing in one minute. In addition to direct measurement, it is possible to calculate this important indicator of ventilation based on the value of the forced expiratory volume in one second (FEV_1), where MVV = FEV_1 x 35. The ratio of MV and MVV is called breathing reserve index (BRI), and values greater than 0.85 at W_{max} indicates inefficiency ventilation (12).

The pattern of the airway response to exercise is mainly determined by the intensity of exercise and airways caliber. In healthy subjects, exercise has bronchodilator effects. The exact mechanism of this effect is unknown. It is proposed that an increase in V_T leads to stretching of muscle fibers in the airway wall, thus reducing the ability for effective contraction (13). In addition, the release of PGE_2, PGI_2 (14, 15) and NO and the inhibition of cholinergic activity are possible mechanisms for the physiologic bronchodilation during exercise. In children with respiratory diseases, these physiologic mechanisms can be compromised.

Patients with severe obstructive ventilatory impairment have static hyperinflation, defined as the residual volume (RV) and total lung capacity (TLC) ratio. It was previously shown that static hyperinflation is a significant negative predictive factor for exercise intolerance in patients with obstructive lung diseases (16). In these patients, progressive effort leads to an additional increase in lung volumes due to dynamic hyperinflation. As a result of these impairments, the MV for the degree of VCO_2 (respiratory equivalent for CO_2) is increased. Given the dependence of MV on Vt and respiratory rate, it is clear that a paradoxical decrease in Vt instead of a physiological increase in progressive effort leads to exhaustion of the breathing reserve and thus to inefficient ventilation and oxygenation. Pulmonary resistance depends on airway and tissue resistance. Through an increase in the mean lung volumes, the airway resistance decreases but may also slightly increase by increased flow (17). An increase in the lung elastic recoil and increased blood flow in the lung lead to decrease in tissue resistance with breathing frequency. A comparable result caused by increased airway resistance, with good responsiveness to inhaled bronchodilators, may occur in children who exhibit EIB.

5. EXERCISE-INDUCED BRONCHOCONSTRICTION

Transient bronchoconstriction and an increase in airway resistance during exercise occur in some healthy children and also in children with asthma. EIB occurs in 8.6-12 percent of healthy children aged 7-17 years, and 40-80 percent of children with asthma may have some degree of EIB (12, 18). Although EIB is

more common in children without adequately controlled asthma, it sometimes can be the only manifestation of disease. Results from a recent survey in the United States showed that the three most frequently reported symptoms in children with asthma and EIB were cough (62.3 percent), shortness of breath (61.4 percent) and wheezing (52.5 percent) (19). These symptoms are mostly mild, usually reaching a maximum 10 minutes after the exercise and might only occur in specific environments, such as ice rinks or indoor swimming pools. Johansson *et al* (2) showed that the prevalence of EIB in a general adolescent population (mean age 14.2 years) is 19.2 percent regardless of gender. Among adolescents in this study who had symptoms, a random subsample underwent an exercise test. There were no significant differences in nutritional status, lung function or previous medical history with respect to self-reported respiratory symptoms during exercise. In a recent study, Mainardi *et al* (20) showed that EIB is more prevalent in low-income neighborhoods. They suggested that EIB may indicate susceptibility to rapid-onset exacerbation and may be a useful indicator for urgent medical visits.

In rare cases, severe episodes of EIB can be followed by respiratory failure and even death (21). If these respiratory symptoms occur after physical exercise in children without a previous diagnosis of asthma, they may raise clinical suspicion of asthma. It often affects the quality of life and frequently results in withdrawal from physical activity. Even elite athletes, particularly those in winter sports, may have a high incidence of EIB. Its prevalence may be up to 50 percent in cross-country skiers (22).

According to an official American Thoracic Society (ATS) statement, the diagnosis of EIB is established by changes in lung function provoked by exercise not on the basis of symptoms. The criterion for the percent decrease in FEV_1 used to diagnose EIB is more than 10 percent. A joint task force of the European Respiratory Society (ERS) and European Academy of Allergy and Clinical Immunology (EAACI) defined exercise-induced asthma (EIA) as symptoms and signs of asthma occurring in an asthmatic after exercise, whereas EIB was defined as a reduction in FEV_1 of at least 10 percent after a standardized exercise test (23).

5.1. Pathogenesis of EIB

Increased metabolic needs in exercising muscles lead to higher VO_2 and an adaptive augmentation in minute ventilation. Higher minute ventilation and mouth breathing leads to reduced warming of inspired air and increased water loss. EIB occurs predominantly after the cessation of a short period of hyperpnea and lasts from 30 to 90 minutes in the absence of treatment. Compared to non-athletes, high-level endurance athletes have an increased prevalence of EIB (24). Although the exact mechanism is unknown, two overlapping hypothesis are currently considered.

The first described mechanism is the osmotic hypothesis, which suggests that hyperventilation leads to dehydration of the airway surface, which is a stimulus for water to move out of epithelial cells and results in a loss of cell volume. Dehydration leads to an increase in the intracellular ion concentration (25), which has a proinflammatory effect. The second hypothesis involves airway cooling by inspired air, which transiently decreases bronchial blood flow (26). Airway narrowing that occurs 10-15 minutes after the beginning of exercise or during breaks results from rewarming, induced vascular engorgement and airway edema (27). Sole cooling and rewarming without hyperventilation was not shown to induce EIB in an animal model (28). Hyperventilation with cold dry air produced a smaller increase in airway blood flow than did hyperventilation with warm dry air (29). Stensurd *et al* (30) showed a significant increase in the VO_2 peak and the peak running speed in patients with previously established diagnosis of EIB; these changes occurred through an increase in the relative humidity of the environmental air from 40 percent to 90 percent. Couto *et al* (31) measured the exhaled breath temperature (EBT) in asthmatic and non-asthmatic elite swimmers before and after training to evaluate the cooling of airways as a possible mechanism for EIB. Although EBT significantly increased in all swimmers, asthma was not shown to be a predictor of change in EBT. The authors suggested that the increase in EBT that results from respiratory heating loss is a physiological response to exercise. These findings all indicate that airway drying is the primary stimulus for EIB. The most probable scenario is that epithelial cell shrinkage and cooling/rewarming processes coexist.

Exercise and EIB seem capable of triggering epithelial damage and an extensive inflammatory response (32). Increased osmolarity stimulates mast cell degranulation and the release of both preformed mediators, such as histamine, and newly formed mediators, such as eicosanoids (33). It was shown that the inflammatory cell count was increased in healthy subjects exercising at a moderate intensity for 2 h in a dry and cold environment (34). An increase in urinary LTE_4 excretion after an exercise challenge has been demonstrated in patients with asthma (35). The concentration of cysteinyl leukotrienes (CysLTs) in the exhaled breath condensate, which was obtained noninvasively, was higher in asthmatic children with EIB than in patients without EIB. A significant positive correlation was shown between baseline CysLT levels and the maximal FEV_1 decrease after exercise (ref 5). Hallstrand *et al.* (36) showed that inhalation of hypertonic saline, which imitates the natural process of epithelial dehydration during exercise, leads to epithelial damage. The analysis of induced sputum showed a relationship between the percentage of epithelial cells at baseline in induced sputum and the severity of EIB. They also successfully demonstrated that the levels of CysLTs are associated with epithelial cell release into the

airways. This is related to the increased expression of phospholipase A group X in alveolar epithelial cells and alveolar macrophages, which play key regulatory role in CysLT synthesis (37).

Airway inflammation is accentuated by allergen and airway pollution exposure. BAL and bronchial biopsies studies (38, 39) showed increased neutrophilia in sport participants involved in any type of endurance training. On the contrary, an increased eosinophil and lymphocyte count is related to exposure to environmental factors, such as chlorine compounds in swimmers or carbon fuel exhaust in ice skaters. The coexistence of rhinitis may also have a negative influence on the development of EIB due to increased mouth breathing and insufficient air conditioning in the upper airways (40).

5.2. Exercise testing for measurement of airway hyperresponsiveness in asthma

Several bronchial challenge tests are commonly used in lung function laboratories to diagnose bronchial hyperresponsiveness (BHR). The diagnosis of EIB can be confirmed in patients with exercise-induced symptoms in whom BHR has been established by bronchial provocation tests. Reversibility in response to inhaled bronchodilators, preferably inhaled $beta_2$ agonists, is a common test in clinical practice. A positive test is indicated by an increase in FEV_1 greater than or equal to 12 percent compared to baseline values, which is a direct confirmation of BHR. Bronchodilators can be administered by a metered dose inhaler, nebulizer or dry powder inhaler.

The direct methacholine challenge test is a well-established dose-response test, and it is more useful in excluding a diagnosis of asthma than in establishing one (21). It shows bronchial muscle functionality through the direct action on airway smooth muscle. In athletes who did not receive any inhaled corticosteroids (ICS) and in those who have been treated with ICS for less than 3 months, the provocative concentration that causes a 20 percent decrease in FEV_1 (PC_{20}) should be less or equal than 4 mg/ml. For those patients who received ICS more than 3 months, PC_{20} should be less than 16 mg/ml (41).

The response to an indirect challenge may be normalized in patients treated with inhaled corticosteroids and bronchodilators. The indirect bronchial challenge tests act on neurally mediated pathways, the neuropeptide release from sensory nerves and the mediator release from inflammatory cells. Challenges that affect both of these pathways, are considered more specific than those that directly affect smooth muscle (42). These tests are exercise testing, eucapnic voluntary hyperpnea, the dry-powder mannitol test and the nebulized hypertonic saline (4.5 percent) test (21, 42, 43).

An exercise challenge test (ECT) is the most commonly used indirect challenge and the first to be standardized (44). It is suggested that ECT should be performed in the environment that usually causes symptoms of EIB (40). In pediatrics, severe airflow limitation (FEV_1 less than 50 percent) is practically the only absolute contraindication for ECT. A controlled free-run test lasting 6 minutes is suitable for very young children, but the running duration is limited with age (12). Airflow limitation can develop earlier and last for a shorter time than after a standardized ECT in older children and adults. The preferred mode of ECT in older children is CPET performed on either a cycle ergometer or a treadmill. Although CPET allows consideration of the mutual influence of different organ systems during physical exercise, the measurement of pulmonary gas exchange is not required to evaluate EIB.

ECT is mostly performed in an air-conditioned room with an ambient temperature below 25°C and low relative air humidity (less than 50 percent). Treadmill or bicycle ergometer protocols are comparable (21). The goal is to achieve the target MV quickly and sustain this level for 4 minutes. The target MV should be 40-60 percent of MVV. The target work rate (in Watts) to achieve the target MV can be calculated using different equations (21). The work rate is set to 60 percent of the target in the first minute, 70 percent in the second, 90 percent in third and 100 percent in the fourth; then, the exercise intensity should be sustained for 4-6 minutes. Another target that can be used to confirm the maximum effort is the heart rate, which should be 80-90 percent of the predicted maximum (220-age in years) (8). The best results can be obtained if the test is hard and brief. A very short warm-up period is essential to avoid refractoriness to EIB.

The primary outcome variable of an exercise challenge test is FEV_1, which is measured before the exercise and then after exercise starting from the 5^{th} minute up to 30 minutes in 5 minutes intervals. The spirometry should be performed with the subject in a seated position, utilizing the principles defined in ATS/ERS Task force (45). A post-exercise exercise decrease in FEV_1 of more than 10 percent at each time interval from the preexercise baseline FEV_1 is considered to be confirmative of the presence of EIB (21, 42). The severity of the FEV_1 drop compared to the preexercise values can be graded as mild if the decrease is between 10 percent and 25 percent, moderate if it is in the range between 25 percent and 50 percent and severe if it is above 50 percent (46). The results from some other studies suggested that a decrease in the FEV_1 of 15 percent appears to be more diagnostic (47). In younger children (3-6 years old), who cannot perform CPET, the $FEV_{0.5}$ value that is measured after a free-run test is a better index than FEV_1 for describing a positive ECT (12).

In recently published research, Sanchez-Garcia *et al.* (48) evaluated which test has the best predictive

value in detecting BHR in pediatric patients with EIB. They tested a relatively small and homogenous group (N=45) of patients with previously diagnosed asthma that primary performed a methacholine test, followed by a mannitol test; the latter resulted in the best detection of BHR. Some other biomarkers are also used to evaluate the positive exercise challenge test. Kruger *et al*. (49) evaluated the utility of hyperpolarized He-3 MRI in detecting the regional lung ventilated volume (Vv) in patients with EIB. They showed that after an exercise challenge, Vv decreased to a greater extent than FEV_1 in patients who were treated with montelukast for EIB compared to patients who received a placebo. That finding led to the conclusion that an evaluation of the regional ventilation with imaging potentially provided a more specific biomarker for the evaluation of EIB than did FEV_1.

5.3. Treatment of EIB

The goals of asthma management in athletes who experience EIB should be similar to non-athletes: regular follow-up visits, good compliance to therapy, individualized therapeutic protocols, avoidance of environmental exposure, recognition of co-morbidities and prevention of asthma-related exacerbations and hospitalizations (23, 50, 51). Although the different treatment modalities should prevent EIB and enable children to be physically active, in athletes, the treatment should facilitate participation in sports activity with minimal symptoms (46). This goal can be achieved by nonpharmacologic and pharmacologic therapy.

5.3.1. Nonpharmacologic treatment

In all patients with episodic EIB, several nonpharmacologic therapies may induce refractoriness of airways and diminish known pathophysiological mechanisms that lead to wheezing symptoms. Warm-up exercise can result in the attenuation of EIB in more than half of the population. This effect lasts 1-2 h, during which bronchoconstriction is less likely (24). This refractory period probably develops as a result of tachyphylaxis of airway smooth muscles to mediators that induce bronchoconstriction. Larson *et al* (52) showed that repeated challenge with mannitol (as a substitute for exercise testing) is associated with diminished release of mast cell mediators of bronchoconstriction, which results in the refractoriness of airways to exercise. The warm-up exercise that is the most appropriate for preventing EIB includes high-intensity and variable intensity intervals before the planned exercise (53, 54). Training programs improve general conditioning, which also has beneficial effects in decreasing the minute ventilation for an existing workload. That change led to less dehydration and cooling of airway mucosa.

Training under inappropriate weather conditions, such as very cold or dry air or in areas with high levels of air pollution or high concentrations of allergens, in sensitized persons may be a contributing factor for EIB. Warming and humidification of inspired air by facemasks is routinely advised in children with EIB in cold weather (46). Breathing through the nose should be favored to preserve the true function of the upper airways – to humidify and warm inspired air (55).

Airway function can also be affected by ozone, nitrogen dioxide, elemental carbon and ambient particulate matter derived from tobacco smoke and mineral fuel combustion. In urban environments, fine particles (less than 2.5 μm in aerodynamic diameter) and ultrafine particles (less than 0.1 μm), which have a size that makes them respirable particles, are mostly generated by traffic from diesel exhaust (56). Persons with asthma or EIB are more susceptible to air pollution and should avoid traffic exposure during exercise. Chlorinated indoor swimming pools should be properly ventilated to decrease the air concentration of chloride-based compounds, such as chloramines.

Dietary modification may have some influences on EIB. Several studies showed beneficiary antioxidant effects of vitamin C in decreasing BHR (57, 58). In animal studies, a single oral dose of vitamin C decreased the plasma levels of histamine, and its deficiency may cause decreased production of PGE_2, which may have a protective effect on EIB by causing smooth muscle relaxation. It was shown that a single oral dose (1-2 g/day) rapidly elevated the levels of vitamin C in the nasal mucosa and epithelial lining fluid. A recent meta-analysis identified 3 placebo-controlled trials that studied the effect of vitamin C on EIB (59). The pooled data from 40 participants indicated a 48 percent reduction in the FEV_1 decline after ECT when vitamin C was administered before exercise. Clinical practice guidelines recommend dietary supplementation of vitamin C for those patients motivated to use dietary interventions to control EIB (46, 55).

Few studies evaluated the effects of a low-salt diet on the mean percent decrease in FEV_1 after ECT (60). A smaller decrease was observed in patients in whom a low-sodium diet was maintained for 1-2 weeks compared to patients who did not receive it (61). Having in mind that low sodium intake is a good nutritional habit, it seems worthwhile to try implementing this diet in therapeutic regimes in patients, especially athletes, who experience EIB (46, 51).

Mickleborough *et al* (62) evaluated a relatively small group of elite athletes with EIB and showed that the daily intake of fish oil for 3 weeks did not have affect the preexercise or postexercise lung function but significantly reduced inflammation and bronchial reactivity. Polyunsaturated fatty acids derived from fish oil inhibit metabolism and the synthesis of cytokines implicated in the development of EIB and may be a potentially useful adjunctive treatment modality.

5.3.2. Pharmacologic treatment

Wheezing during exercise in children is frequently associated with underlying persistent asthma, but it should never result in the cessation of sports activity. The most common therapeutic approach for preventing EIB is prophylactic intermittent treatment with bronchodilators. If bronchodilators are used frequently, then regular treatment with controller medication should be initiated, which can mostly attenuate EIB (63).

5.3.2.1. Short-acting beta$_2$ agonists

Short-acting beta$_2$ agonists (SABA) are effective in preventing EIB when used 5 to 20 minutes before exercise (23, 46, 64). The effects lasts up to 2 h, but in 15-20 percent of patients with EIB, SABA may fail to prevent bronchoconstriction. The currently used SABAs have no performance-enhancing effects in athletes regardless of a previous diagnosis of asthma (24).

A recent Cochrane review evaluated the results of 59 studies that assessed the effects of beta$_2$ agonists on EIB (65). Compared to placebo, to SABA and long-acting beta$_2$ agonists (LABA) were shown to be effective at reducing the postexercise decrease in FEV$_1$, without a difference in the occurrence of side effects. The long-term use of SABA may result in the loss of asthma control, which may compromise its effects and increase BHR. The precise mechanism of tachyphylaxis is unclear, but it is mostly related to the polymorphism of beta$_2$ receptors, its internalization or reduced production and uncoupling from secondary messengers (66).

Changes in international sports legislation led to a 27 percent reduction in the reported usage of SABA between the 2000 and 2004 Olympics (50). This decreased occurred because all athletes had to have documented EIB by either ECT or some other tests of BHR. Nevertheless, the percentage of athletes with EIB who used ICS continuously with SABA intermittently gradually increased from 46.1 percent in 1996 to 77.2 percent in 2006. The World Anti-Doping Agency allows inhaled albuterol, LABA (salmeterol and formoterol) and all registered topical glucocorticoids (67).

5.3.2.2. Mast-cell stabilizing agents, anticholinergics and antihistamines

If SABA is not effective in preventing EIB, then addition substitution of mast-cell stabilizing agents, such as cromolyn or nedocromil, may be indicated (51). Although cromolyn and nedocromil have comparable efficacy in preventing EIB, especially immediately before exercise, their rare use is a consequence of the lack of availability in many European countries and the USA (23, 68).

Short-acting anticholinergic treatment is frequently combined with a beta$_2$ agonist to treat asthma exacerbation. In patients with EIB who require frequent prophylactic treatment with SABA, it is suggested that ipratropium bromide may be helpful in reducing exercise-induced symptoms (23, 46).

Antihistamines may improve symptoms in allergic persons with EIB, although its efficacy was not proven in clinical studies. It should not be recommended for a nonallergic person who exhibits EIB (46).

5.3.2.3. Inhaled corticosteroids, long-acting beta$_2$ agonists and montelukast

When SABA is used more than four times per week to prevent EIB, the use of chronic therapy for better symptom control is justified (69). Inhaled corticosteroids (ICS) are the mainstay treatment of persistent asthma. This treatment is mostly sufficient to establish control of exercise-induced symptoms. Attenuation of EIB starts after a week, but in most patients, full control is established after several months of therapy. There are different opinions as to whether the decrease in exercise-induced symptoms and postexercise FEV$_1$ correlates with the dose of regularly used ICS, but it seems reasonable to believe that moderate to high doses may have better protective effects compared to those of low doses (70, 71). Adherence to therapy with ICS leads to better asthma control. Discussing the results of ECT in preschool children with their parents did not result in an improvement in adherence to maintenance medication (72).

Stelmach *et al* (40) showed that the control of both asthma and the associated EIB could be achieved by the chronic use of several different, regularly used controller therapies. The lowest postexercise FEV$_1$ in this group of patients resulted from the regular oral use of montelukast, followed by a low dose of inhaled budesonide (BUD). Combined therapy with ICS and montelukast is showed to be superior to each therapy alone. Another study evaluated the effects of montelukast as an add-on therapy in decreasing the BHR in asthmatic children. A week of treatment with BUD decrease the BHR measured by ECT and a mannitol test (73). Adding montelukast to BUD led to a further decrease in BHR in this small group of patients.

Adding LABA to ICS is a possible next step in asthma management. Salmeterol and formoterol significantly improved asthma management, but its chronic use is associated with increased incidences of serious complications. Although it was shown that fluticasone propionate (FP) provided protection following ECT, the combination of FP and salmeterol was significantly better at reducing he lung function decrease after exercise in children and adolescents with asthma (74). Adding formoterol to BUD therapy did not contribute significantly to a further decrease in FEV$_1$ beyond that achieved with the initial treatment with BUD (39). Expectations that LABA will provide a more sustained effect in controlling

EIB are controversial (75). It is suggested that a single therapy with LABA alone is not recommended and that LABA should be added selectively (46, 75). A recently published study showed that the combination of BUD/formoterol on demand improves EIB in patients with asthma better than SABA treatment on demand. The combination was also shown to be non-inferior to regular BUD treatment (76).

6. CONCLUSION

Exercise-induced respiratory symptoms are common in childhood. Ventilatory inefficacy, which is, in most cases a reason for exercise intolerance, frequently results in wheezing as a symptom of bronchoconstriction. Recent advances in the standardization of protocols for diagnosis allow appropriate therapeutic regimes, suitable pharmacologic treatment and undemanding non-pharmacologic interventions that finally should result in the continuation of physical activity and participation in sports by children.

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