

The breathless adolescent asthmatic athlete

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Summary

The present review article concerns physical activity and sports in asthmatic adolescents. Exercise induced asthma (EIA) is found in 8-10% of a normal child population and in approximately 35% of children with current asthma as reported from a population based birth cohort study.

The mechanisms of EIA are related to markedly increased ventilation during exercise, causing increased heat and water loss through respiration, leading to bronchial constriction.

In athletes and especially in endurance athletes, the repeated daily physical activity during training will over time cause epithelial damage and increase inflammation in the respiratory mucosa. With increased exposure to environmental agents as cold air in skiers and chlorine compounds in swimmers, the athlete may contract symptoms and signs of asthma and bronchial hyperresponsiveness, either worsening an existing asthma or causing symptoms in a previous healthy adolescent athlete.

There are several causes of breathlessness in adolescents including EIA, vocal cord dysfunction, poor physical fitness and others, important to consider in the diagnostic procedure.

The asthmatic athlete should follow the same guidelines for treating his/her asthma as the ordinary asthmatic patient with concern made to the special diagnostic rules given for the use of asthma drugs in sports, especially for inhaled β_2 -agonists.

Introduction

Sports activities and physical activity in general are important for the majority of school children and adolescents. Active physical activity has effect upon development, psychological function and growth (1). Strunk et al reported in 1989 that fitness was related to psychological function in asthmatics children (2). Children usually vary their activity between vigorous activity and low intense activity continuously. Bailey reported that children had low intensity activity 77.1% of the time, compared to high intensity 3.1% of the time, but varying continuously between the two (3). For the asthmatic child it becomes important to master exercise induced asthma (EIA) without being dependent upon planned pre-medication before planned exercise training. Thus anti-inflammatory treatment controlling the asthma becomes important for the daily life activities of children and adolescents with asthma. Recognising this, treating and preventing EIA has become one of the main objectives of treating asthma among all international and national guidelines for the treatment of childhood asthma (4-6). This has obvious relevance also to the asthmatic adolescent actively participating in sports.

Prevalence of exercise induced asthma (EIA) and exercise induced bronchoconstriction (EIB)

We define exercise-induced symptoms and signs of asthma occurring after intensive physical exercise as exercise induced asthma (EIA). The reduction in lung function (FEV₁) occurring after a standardised exercise test is called exercise induced bronchoconstriction (EIB) (7). A reduction of at least ten per cent in FEV₁ after exercise is the common definition of EIB (7). EIA has been reported to occur

frequently in asthmatic children and adults without anti-inflammatory treatment, and reported in up to 70-80 per cent of non-treated asthmatics (8). In the Oslo birth cohort: Environment Childhood Asthma study, 36.7 per cent of ten year old children with current asthma had a positive exercise test and thus suffered from EIB regardless of type of treatment, whereas in the entire population-based cohort 8.6 per cent had a positive EIB test (9).

Why does exercise cause asthma symptoms (EIA)?

Physical activity increases the need for oxygen and thus increases ventilation and thus the amount of air passing through the airways to and from the lungs. On its passage through the airways, the incoming air is heated to 37 °C and is fully saturated with vapour. This again gives rise to increased water and heat loss through the respiration. Cooling of the airways gives reflex parasympathetic nerve stimulation leading to bronchoconstriction through stimulation of the vagal nerve, initially causing reflex vasoconstriction of bronchial venules to conserve heat, and then at the end of the exercise and the increased ventilation, causes vasodilatation. This causes a combination of smooth muscle constriction and mucosal oedema in susceptible individuals (10), reducing the size of the bronchial lumen with increased airways resistance (11). However, the increased water loss through the increased ventilation is considered to be more important by increasing the osmolality in the extracellular fluid of the bronchial mucosal membranes. S.D. Anderson (12) has shown that the osmotic gradient caused by water loss from the bronchial mucosa, induces water to move extracellularly and through regulatory volume increase causes increases in the intracellular concentration of ions as demonstrated for calcium and inositol

triphosphate (13). This process may lead to mediator release, both newly formed mediators through splitting of phospholipids releasing eicosanoids and also preformed mediators like histamine from intracellular granules thus causing bronchoconstriction. It is suggested that cold air exerts its effect through its low content of water, thus participating in the drying of the respiratory mucosa (12). These mechanisms explain why EIA often occurs shortly after heavy exercise, and not during the maximum exercise intensity, a fact being important in the diagnosis of EIA.

Participation in physical activity and sports and training of asthmatic adolescents

It has been reported that asthma limits the participation of children in physical activity, especially in vigorous physical activity (14). Therefore, optimal asthma treatment is important in order to master EIA and to allow full participation in physical activity, play and sports activities (15). When asthmatic children participate in physical exercise activities and training, their quality of life improves as well as their physical fitness (15), although asthma severity and lung function are not influenced (16). In addition to quality of life and fitness, also the level of physical activity increased after participating in training groups, leading to a more active, and according to the authors, a happier life (17).

With present days modern asthma care, asthmatic 13 year old children from the Oslo birth cohort study were as fit as healthy children and as physically active (18). Thus asthmatic children and adolescents being as physically active and as fit, may

participate in sports activities on an equal level with healthy children provided they receive optimal treatment for their asthma.

Several studies report that when participating in systematic physical training, the asthmatic adolescent or child improves fitness, quality of life and also exercise level (15, 17). This was confirmed by Ram who performed a Cochrane based meta analysis of eight training studies including 226 asthmatics from six years of age (16). They concluded physical training improved fitness as measured by increased maximum oxygen uptake. However, there was no change in lung function. After the publication of Ram, Counil and coworkers reported similar findings, improvement in aerobic and anaerobic fitness in the adolescent training group (mean age 13 years), but no improvement in lung function after 6 weeks of exercise training with high intensive bouts (19). Fanelli et al reported improved quality of life and improved asthma control in the actively training group compared to a non-training group (20). Moreira et al conducted a three month training programme in adolescents (mean age 13.4 years), and found no changes in asthma control, but on the other hand a reduction in total IgE and specific IgE to mites in the training group (21).

On the other hand, Vahlkvist and coworkers reported that newly diagnosed asthmatic adolescents were less fit and had lower levels of high vigorous physical activity than control subjects (22). Starting anti-inflammatory treatment and obtaining better asthma control, increased both fitness and level of vigorous activity after one year of treatment (23). This also shows that level of physical activity in asthmatic children and adolescents may be seen as a marker of asthma control (23).

These later studies thus confirm the meta-analysis of Ram, and all studies conclude that physical training is recommended in asthmatic children.

Why do healthy adolescent athletes develop asthma and bronchial hyperresponsiveness?

Increased prevalence of asthma and bronchial hyperresponsiveness (BHR) have been reported among elite athletes, and especially in endurance sports, most frequently in cross-country skiers and swimmers (24-26). In Olympic athletes a similar pattern was reported for the use of asthma drugs during the Olympic Games (27). In cross-country skiers the prevalence of asthma and BHR was found to increase with increasing age, and the prevalence was found to be higher the longer the athletes had competed (24, 28). Among adolescent swimmers, however, we found a high prevalence of BHR in the ages of 16 to 22 years, both measured by metacholine bronchial provocation and by eucapnic voluntary hyperpnoea (29). Furthermore, a relationship between exposure to chlorinated swimming pools during childhood and adolescence and prevalence of asthma and EIA, suggests that exposure to chlorine and organic chlorine products during physical activity represents an environmental hazard (30, 31).

Bougault and coworkers reported in several articles on swimmers and winter sport athletes. They reported positive metacholine bronchial challenges more often positive in competitive swimmers and winter sport athletes as compared to healthy controls, and most often in swimmers (32). Bronchial challenges to metacholine were found more often positive than tests for eucapnic voluntary hyperpnoea (33). Of particular interest was the finding of increased neutrophil cell counts in induced sputum in both swimmers and winter sport athletes, and that the neutrophil counts correlated to number of training hours per week in both groups (32). Eosinophil counts were increased in swimmers in particular, as also was number of bronchial epithelial cells (32). The relationship to training is of particular interest, and Bougault found that two

weeks rest free of training in swimmers induced a reduction in bronchial responsiveness both to metacholine and Eucapnic voluntary hyperpnoea. Eight out of 12 swimmers with bronchial hyperresponsiveness during training had no bronchial hyperresponsiveness during rest. In this particular study, no airway inflammation was detected as measured by exhaled nitric oxide and induced sputum analyses, and no change in airway inflammation from training to rest occurred (34).

The first report that BHR increased after heavy exercise was made on adolescent swimmers (12-18 years of age) swimming 3000 meters. The increase in bronchial responsiveness from before to after the heavy exercise correlated with the level of exercise load (increase in blood lactate) in both asthmatics and healthy swimmers (35). Later Sue Chu et al showed that adolescent cross country skiers (ski-gymnasts) during one competitive winter season developed signs of inflammation (lymphoid follicles and deposition of tenascin) in their bronchial biopsies independent of being asthmatics or not (36). These findings were later confirmed in animal studies.

Mice, exercised by running, developed signs of inflammation and epithelial damage in their lungs as compared to sedative mice (37). Alaskan sledge dogs were examined by bronchoscopy and bronchoalveolar lavage before and after a sledge race across Alaska and with similar findings (38). Also in humans these findings were recently replicated as increased levels of bronchial epithelial cells were found in induced sputum of amateur endurance runners from before to after repeated half-marathon races, in addition to apoptosis of bronchial cells after the races. Also increased serum levels of clara cell protein 16 and increased supernatant interleukin 8 levels of induced sputum were found demonstrating increased airway inflammation caused by participation in the half marathon races (39).

These animal studies agree with the findings in induced sputum in swimmers and cold weather athletes reported by Bougault and coworkers as already mentioned above (32).

Thus, training with a heavy exercise load will through the increased ventilation give increased airways wear and tear on the respiratory epithelium with airway inflammation and epithelial damage as a result.

Water movement across cell membranes was stated as an important part of the pathogenesis of EIA (12). Aquaporin is a channel for aqueous water transport driven by osmotic forces generated by sodium and chlorine ions and expressed in respiratory subepithelial glandular cells and alveolar type 1 cells of the lungs (40). It has been shown that mice lacking the gene for the aqueous water channel aquaporin (Aqp) 5 exhibit methacholine-induced bronchiolar hyperreactivity when compared to normal mice (41). Park et al recently reported that in healthy athletes suspected of having EIA, a relationship was found between metacholine bronchial responsiveness and diminished pilocarpine induced sweat secretion, tearing rate and salivary flow rate (40). This indicates the possibility of a genetic influence making athletes more susceptible to develop EIA and BHR.

Intensive and regularly repeated training has been shown to influence autonomic regulation with increased sympathetic and parasympathetic activity. Filipe et al demonstrated increased parasympathetic activity in athletes by pupillometry, and significantly higher in endurance runners (42). This is in line with our practical experience that our Norwegian competitive endurance athletes in our National teams respond particularly well to inhaled ipratropium bromide and with a higher reversibility to this drug than to inhaled β_2 -agonists. This is also supported by the reports of Knopfli related

both to cross country skiers and to training children (43, 44)..

The environmental factor

The exercising athlete will be more exposed to environmental agents in the surrounding air due to the increased ventilation during exercise. This is supported by the studies of children in swimming pools by Bernard et al (30), and by measurements of bronchial responsiveness in adolescent Norwegian competitive swimmers (29) as well as by increased inflammatory markers in Finnish competitive swimmers (46).

The environmental exposures will differ between different sports. Cross country skiers are repeatedly exposed to cold air (24), athletes training and competing in ice shrinks may be exposed to NO_x from the freezing machinery as well as to ultrafine particles from the polishing machines (47), corresponding to reports of high asthma prevalence among ice-hockey players (48) and figure skaters (49).

In a study from South-California increased prevalence of asthma was found in children participating in sports in areas with high environmental pollution due to ozone. The study concerned 3535 children from 12 areas in South-California, six areas with a high level of pollution (ozone) and six with low pollution levels. After a follow-up of five years, it was found that children actively participating in more than three types of sports in areas with high ozone levels had an increased relative risk of asthma of 3.3. To participate in sports in areas with low ozone levels gave no increased risk of asthma. Time spent outdoors in areas with high ozone levels were related to increased risk of asthma, but not so in areas with low ozone levels (50).

This demonstrates, together with the studies from Belgian swimming pools, that it is necessary with strict criteria for environmental exposures in sporting arenas where children and adolescents train and compete. To set high demands on the

environmental conditions for sports may have important health consequences for the athletes.

There are two main phenotypes of asthma in endurance athletes. First there are athletes with asthma from early childhood, often accompanied by allergy. Secondly, there are those athletes who contract their asthmatic symptoms through the repeated heavy training, and competitions because of their sport. The latter may not have the obvious asthmatic symptoms caused by acute episodes of bronchoconstriction, but rather cough and phlegm over prolonged periods of time, and often provoked by repeated competitions and viral infections. The latter phenotype is not unlike chronic persistent asthma.

Asthma occurring in relationship to competitive sports may occasionally have fatal outcome. An American study identified nationwide deaths related to competitive sports activities over a seven-year period. Out of 263 sports related deaths, 61 deaths were asthma related provoked by competitive sports. Among these 61 deaths most occurred in boys younger than 20 years, and only one of the athletes who died used inhaled steroids, two used disodium cromoglycate. The remainder used no controller asthma medication, thus underlining the necessity of an optimal asthma care in asthmatic athletes (51).

Diagnosis and differential diagnosis of exercise induced asthma in adolescent athletes

The diagnosis of EIA may be made by a standardised exercise test. The standardisation of the test is very important for the outcome. The exercise load should high, preferably up to 95% of maximum exercise load for the adolescent as assessed

by heart rate (52). The test should also be standardised as regards environmental temperature and humidity (53). The exercise test has high specificity for asthma, but lower sensitivity, especially when the adolescents are treated with inhaled steroids. Testing for direct bronchial responsiveness, through bronchial challenge with metacholine, has higher sensitivity, but lower specificity for asthma (28, 54, 55). The metacholine test represents a useful measure of the respiratory problems of the athlete.

It has been stated that sports specific field exercise tests are much more sensitive in athletes (56), but this could not be verified in another study (28). Also eucapnic voluntary hyperpnoea (57) although being an indirect test of bronchial responsiveness, is a sensitive test of bronchial responsiveness in athletes. This test is physically demanding to perform (29). Inhalation of mannitol has also been suggested as a substitute measure of EIA (58). The mannitol test may give information about the indirect bronchial responsiveness comparable to EIB, but will give no information about physical fitness, motor skills and motor development that is also obtained by a trained observer through an exercise test in children and adolescents.

EIA usually occurs shortly after a heavy exercise. Typically the bronchial constriction reaches its maximum 6-10 minutes after the exercise, and the dyspnoea will be expiratory. If the respiratory distress occurs during maximum exercise and is inspiratory, exercise induced vocal cord dysfunction (VCD) may be a more probable diagnosis. The condition was first described by Refsum (59), then later by McFadden jr. (60) and in adolescents by Landwehr et al (61). Among well-trained adolescent athletes, and especially among girls this is as frequent diagnosis as EIA. This differential diagnosis is very important, as asthma treatment will have no effect upon this condition. One should be aware of that EIA may coexist with VCD (62). There is

no uniform consensus defining VCD, but this definition has been proposed: an intermittent extrathoracic airway obstruction mainly during inspiration, leading to dyspnoea of varying intensity (63). Exercise induced VCD should be suspected when the respiratory stridor occurs during maximum exercise intensity and is inspiratory. A maximal inspiratory flow at 50% of forced vital capacity (MIF50)/maximal expiratory flow at 50% of forced vital capacity (MEF50) ratio <1 after a metacholine bronchial provocation has been taken as a suggestion of VCD (63). A maximum intensity treadmill run, when audible inspiratory stridor occurs during maximum intensity, can confirm the diagnosis. The diagnosis is further verified by continuous laryngoscopic exercise test (64, 65). There are different treatment modalities for exercise induced VCD, and even surgery through endoscopic supraglottoplasty has been described as useful in selected patients (66). Also exercise induced hyperventilation with increased end-tidal CO_2 at the end of exercise has been described as a differential diagnosis to EIA in children and adolescents (67)

Other not uncommon differential diagnoses to EIA have been given in Table 1.

Among these, poor physical fitness lower than the expectations should be mentioned.

This includes obesity, which may represent a differential diagnosis to EIA in the common asthmatic patient, but rarely in athletes.

Treatment of exercise induced asthma in adolescent athletes

Asthma in adolescent athletes should be treated in the same way and according to similar guidelines as asthma in other adolescents. However, special precautions must be taken related to the rules, given by the doping authorities with respect to the use of inhaled β_2 -agonists and inhaled steroids in sports. These rules are often changed, sometimes annually, even if the changes may be minor. However, the physician

caring for children and adolescents who are active in sports should know and be updated on these rules (Table 2 and 3).

According to the common guidelines mild asthma should be treated with inhaled β_2 -agonists when needed (prn). However, inhaled β_2 -agonists were subject to restrictions for the use in sports, and mild asthmatics would not satisfy the given rules. Then, from January 1st 2011 the World Anti Doping Association (WADA) again changed the rules. From this date inhaled salbutamol may freely be used with a maximum daily dosage less than 1600 μg . This is also the case for inhaled salmeterol without specifying any maximum dosage. On the other hand, for the use of inhaled terbutaline and inhaled formoterol, the old rules still holds, and application for a therapeutic use exemption is necessary for the use of these drugs (TUE). WADA has given no reasons for the change of rules, and there is no scientific reason that the inhaled β_2 -agonists from one pharmaceutical company should be free, whereas the drugs from other pharmaceutical companies should be restricted. From January 1st 2011 all inhaled steroids are free for use.

When bronchodilation is needed, inhaled ipratropium bromide may also be tried before exercise or competition, as this drug has no restrictions related to sports. Also montelukast has no restrictions and can be tried, both due to its bronchodilating and its partly anti-inflammatory effect. With the presence of bronchial hyperresponsiveness and respiratory symptoms, inhaled steroids should be tried.

Inhaled steroids are among the drugs, which have now become free from January 1st 2011, leaving the decision of use to the physician. If the athlete satisfies the new rules for using also the restricted inhaled β_2 -agonists, treatment can be given after common guidelines, but with the use of TUE for certain drugs (Table 3). The common guidelines for controlling and relieving medications should be followed. One should

also remember that prescribing treatment is part of the diagnostic process. If treatment fails, the diagnosis should be reconsidered.

How to help athletic adolescents with asthma and BHR to master their asthma without conflict with the rules of sports and doping authorities?

One should be aware of the special rules set up for the use of asthma drugs in sports. When an athlete consults you as a physician because of respiratory problems during physical activity, one should not prescribe the restricted drugs until a thorough examination has been made. This is very important for the athlete in order to avoid problems with the doping authorities.

First, the physician should know the valid rules for the use of asthma drugs in sport. Changes in the rules are often made at the time of change of the year. The valid rules can be found on the web sites of the World Anti Doping Association (WADA) and on the web sites of the national anti doping authorities. From this year on the new rules are given in Table 3.. Internationally competing athletes use a web-based system to inform the doping authorities where they will stay at any time (called ADAMS).

Within this system there are specific forms for TUE to be completed. Printouts of lung function examinations and measurements of BHR can be scanned and attached to these forms. For some asthma drugs the athlete must apply through a TUE, other drugs are now completely free (inhaled steroids, salbutamol and salmeterol).

Declarations of use (DOU) were introduced from 2010, but have now been abolished.

When submitting a application for TUE, the athlete will receive approval (or the opposite) within a few weeks after submitting the form.

For the use of certain inhaled β_2 -agonists, there are objective requirements to be met. The rules are strictly abided. Systemic β_2 -agonists are not at all allowed. To use the inhaled β_2 -agonists terbutaline and formoterol, clinical symptoms of asthma and in addition objective measurements as given in Table 3 are required.. The rules for the different drugs are given in Table 2.

Athletes on a national level will not have to apply for a TUE. However, they will have to satisfy the same rules to use the drugs. If the athlete is controlled by a doping test, the doping authorities will collect information from the relevant physician.

It is the responsibility of the athletes themselves to know the rules and to abide by these. However, the physician caring for adolescent athletes should know the rules to be able to offer care in accordance with the rules and thus avoid any problems for the athlete.

It is important to offer the correct treatment for the single adolescent athlete, in accordance with his/her disease severity and in accordance with the rules of the sport.

We want to help the athlete with asthma, in spite of the illness, to fulfil his/her possibilities for participation in physical activity and sports. Today we are able to control asthma and help the patient to optimise his asthma control and master his EIA in such a way that the adolescent athlete with asthma may compete at the international top level.

Table 1. Possible differential diagnoses to exercise induced asthma

Diagnosis	Clinical presentation in the athlete
EIA	Symptoms occur shortly after (sometimes during) physical exercise. The dyspnoea is of expiratory type. By auscultation: Rhonchi and sibilating rhonchi. Respiratory retractions. Gradual improvement occurs either spontaneously or after inhaled bronchodilator.
Exercise induced vocal cord dysfunction (VCD)	Symptoms occur during maximum exertion. Symptoms disappear when exercise is stopped unless the patient continues to hyperventilate. The dyspnoea is of inspiratory type. There are audible inspiratory sounds from the laryngeal area and no signs of bronchial obstruction. No effect of pretreatment with inhaled bronchodilator (65).
Exercise induced hyperventilation	Hyperventilation with respiratory dyspnoea and increased end-tidal CO ₂ (67).
Exercise induced arterial hypoxemia (EIAH)	Occurs in well-trained athletes with high maximum oxygen uptake. It is primarily thought to be due to diffusion limitations and ventilation-perfusion inequality. Incomplete diffusion in the healthy lung may be due to a rapid red blood cell transit time through the pulmonary capillaries (68).
Swimming induced pulmonary oedema (SIPE)	May occur after heavy swimming exercises with symptoms of haemoptysis, cough and respiratory distress. Reduced diffusion capacity (TLCO) for up to weeks afterwards (69)
Other chronic lung diseases	Reduced baseline lung function may reduce physical performance due to limitations in air flow and lung volumes (70).
Other general disease	Chronic heart diseases and others general disorders
Poor physical fitness including obesity	Related to expectations. High heart rate after low grade exercise load

Table 2. Overview of the asthma drugs for which the athlete must apply for the use through a therapeutic use exemption (TUE) from 1st of January 2011.

Medication	Regulations from January 1 st 2011 according to WADA
Inhaled β_2 -agonists	
Salbutamol	Free use until maximum daily dose of 1600 μg Urinary salbutamol >1000 ng/mL is considered an <i>Adverse Analytical Finding</i> unless proven that this was due to a dose of inhaled salbutamol $\leq 1600 \mu\text{g}$ over 24 hours
Salmeterol	Free use
Terbutaline	Prohibited. TUE necessary
Formoterol	Prohibited. TUE necessary
Other inhaled β_2 -agonists	Prohibited
Inhaled steroids, all	Free use
Combination inhaled steroid + β_2 -agonist	
Inhaled steroid + formoterol	Formoterol prohibited. TUE necessary.
Inhaled steroid + salmeterol	Free use
Inhaled ipratropium bromide	Free use
Montelukast	Free use

Table 3. Diagnostic procedures in the process of diagnosing asthma in sports according to present rules for obtaining a Therapeutic use exemption (TUE) for certain inhaled β_2 -agonists (terbutaline and formoterol).

Diagnostic procedure	Results required by WADA / IOC-MC
Clinical history of respiratory symptoms and clinical examination	Positive clinical history and signs indicative of the presence of asthma
+ One of the following objective tests:	
Lung function: Spirometry with reversibility to inhaled bronchodilator	Increase in FEV ₁ (+12%) after inhaled bronchodilator
Standardised exercise test for EIB or Exercise field test	FEV ₁ decrease of 10% from before to after exercise challenge
Bronchial hyperresponsiveness to metacholine (histamine presently not allowed by IOC-MC)	PC ₂₀ ≤ 4 mg/ml or PD ₂₀ ≤ 2µmol in athletes without inhaled steroids PC ₂₀ ≤ 16 mg/ml or PD ₂₀ ≤ 8µmol in athletes on inhaled steroids for at least one month
Mannitol inhalation test (Airidol® test)	Reduction in FEV ₁ of 15% or more. Determination of PD ₁₅ of mannitol
Eucapnic voluntary hyperventilation test	Reduction in FEV ₁ of 10 % or more
Inhalation of hyperosmolar solutions	Reduction in FEV ₁ of 15% or more

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