

ERS School Course Basics in Asthma



Exercise testing, exercise-induced asthma and sports

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Educational aims

- ▶ To inform about the occurrence of EIA, particularly in top athletes.
- ▶ To describe how EIA can be diagnosed.
- ▶ To describe the pathogenesis of the condition.
- ▶ To familiarise the reader with treatment modalities available to athletes.
- ▶ To make the reader aware of doping regulations in relation to EIA.



Summary

Exercise-induced asthma (EIA) is a general concern for growing children and adolescents, although it now occurs more commonly in top athletes. It specifically affects athletes competing in endurance sports in cold climates. EIA can be diagnosed *via* exercise testing and can be easily treated both prophylactically and before exercise. However, with tight regulations now in force in the sporting world, athletes with EIA have to be sure that they adhere to doping rules. This review aims to briefly review these issues.

"If from running, gymnastic exercises, or any other work, the breathing become difficult, it is called ASTHMA (ασθμα); and the disease Orthopnæa (ορθοπνοια) is also called Asthma, for in the paroxysms the patients also pant for breath."

Aereteus the Cappodocian

The citation above, which is >2,000 years old, shows the long-standing knowledge about the relationship between physical activity and asthma. EIA is a general concern for growing children and adolescents, but also occurs in top athletes in several different types of sports. Traditionally, this has been reported most often in athletes competing in endurance sports in cold climates, and in other environmental hazards like swimming with inhalation of chlorine products in indoor swimming pools. In particular, this has been found among cross-country skiers and swimmers, but also among endurance athletes competing in summer sports. In addition, there is a surprisingly high prevalence of asthma among professional Canadian football players, which was diagnosed by reversibility of lung function to inhaled β_2 -agonists (56%) during a summer training camp [1]. The prevalence of EIA among top athletes has gradually increased. WEILER and coworkers [2, 3] previously reported a prevalence of EIA of 11% among American elite athletes participating in the 1984 summer Olympic Games, whereas, using identical criteria for diagnosis, this increased to >20% among the American participants in the 1996 summer Olympic Games in Atlanta.

Figure 1
a) Vocal cord dysfunction during expiration; b) vocal cord dysfunction during inspiration; and c) supraglottic collapse during heavy inspiration. Reproduced with permission from *Allergy & Clinical Immunology International* 2001; 13: 140–146.



Exercise testing in asthma

The most important method used for exercise testing in asthma is to provoke exercise-induced bronchoconstriction (EIB), which is carried out under standardised conditions. Running provokes EIB in children more easily than cycling. Running for 6–8 minutes provokes a greater decrease in post-exercise forced expiratory volume in one second (FEV₁) than running for shorter or longer time periods. One useful way to standardise the diagnosis of EIA in athletes is to employ a motor-driven treadmill, with an inclination of 5.5%. Once on the treadmill, the speed is rapidly increased until a steady heart rate of ~95% of the calculated maximum is reached, and this should be maintained for 4–6 minutes. The widespread use of inhaled steroids necessitates this level of exercise. Maximum heart rate is calculated approximately by the following formula: 220–the age of the patient. Heart rate can be measured electronically by devices such as the Sport-Tester PE 3000® (Polar Electro Oy, Kempele, Finland). Running is performed at a room temperature of ~20°C and a relative humidity of ~40%. Lung function is measured before running, immediately after cessation of running, and 3, 6, 10, 15 and 20 minutes after running. FEV₁ is usually the lung function parameter employed, and a fall of 10% is usually taken as a sign of EIA.

In addition to diagnosing EIA, the reduction in FEV₁ after standardised exercise may be considered as a measure of non-specific bronchial reactivity and used to evaluate the severity of asthma, as well as the effects of therapy. When adding an extra stimulus to the exercise test, by combining running on a treadmill with the inhalation of dry cold air of -20°C, the sensitivity of the test is markedly increased while simultaneously maintaining a high degree of specificity.

There are several differential diagnoses for EIA, including exercise-induced laryngeal inspiratory stridor and hyperventilation during exercise. These conditions should be carefully considered, as patients with these conditions have been given unnecessary drugs for the treatment of asthma, including both inhaled steroids and β_2 -agonists, which will have no effect. Exercise-induced laryngeal stridor is more common among highly trained female athletes during adolescence. Marked inspiratory stridor during maximal exercise with a flattening of the maximal inspiratory flow–volume curve is typical, in contrast to EIA where dyspnoea occurs after exercise and is

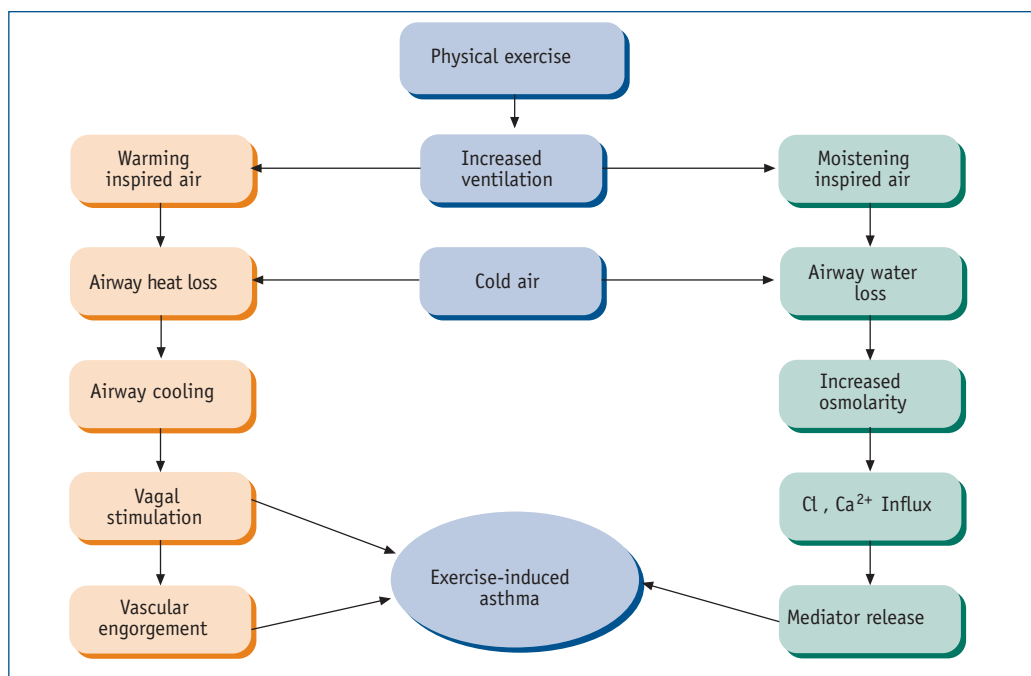


Figure 2
Mechanisms of exercise-induced asthma.

expiratory due to the lower airways obstruction. During exercise, figure 1 shows how the laryngeal orifice of a well-trained female adolescent athlete is well open during expiration, but narrows markedly during inspiration, and, finally, while exercising even more heavily a supraglottic collapse occurs.

Testing for physical fitness employs procedures other than those used for testing for EIB. Several protocols have been developed, depending on the type of illness or if the patient is a healthy athlete. A stepwise increase in exercise load is used, after an initial warm-up period. Oxygen uptake and ventilation are measured. This type of testing is of less importance in relation to asthma as compared to chronic obstructive pulmonary disease. However, the possibility to record tidal breathing curves during running on a treadmill also enables the physician to assess if the airways may limit physical performance.

Pathogenesis of exercise-induced asthma

Presently, two main hypotheses are discussed to explain the relationship between physical activity and EIA (figure 2). One relates to cooling of the airways in relation to increased ventilation during exercise, the other hypothesis relates to increased loss of water from the respiratory tract, also caused by increased ventilation during exercise.

First, GILBERT and MCFADDEN [4] have suggested

that airway cooling due to respiratory heat loss with rewarming by secondary hyperaemia and pulmonary vasodilatation is the probable cause of EIA. Furthermore, due to pulmonary vasoconstriction induced by the cold air, a secondary reactive hyperaemia may occur, with resulting oedema and airways narrowing. Secondly, there is substantial evidence to indicate that EIA is effected through the release of mediators from mast cells and other inflammatory cells of the airways [5]. The mediator release provoked by exercise is the main reason for considering EIA as an indirect measure of bronchial reactivity. The lower respiratory tract is lined by a ciliary epithelium coated by periciliary fluid. During breathing, respiratory vapour loss increases rapidly with increasing ventilatory rate, and increasingly so when inhaling cold air. Air at 37°C, fully saturated with vapour contains 47 mg H₂O per L of air; air at room temperature (22°C), with 50% relative humidity contains 22 mg H₂O per L of air; and air at -10°C, with 50% relative humidity contains only 1 mg H₂O per L of air. Thus, with the high ventilation rates of top athletes (up to >280 L per minute) during exercise, the loss of water is considerable. The main factor causing the mediator release is thought to be the change in osmolarity of the periciliary fluid lining the surface of the respiratory mucosal membranes, caused by respiratory water loss. The increase in chloride ions on the luminal side of the bronchial epithelium is thought to be the stimulus for mediator release. The increased extracellular osmolarity thus leads to influx into the cell, particularly of Na⁺ and Cl⁻. Ca²⁺ follows

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Cl⁻ passively into the cell and this activates phospholipase in the cellular membranes, leading to activation of phospholipase II, thus increasing the output of leukotrienes and causing mediator release [6].

Endurance training and the development of asthma and BHR and environmental factors

An increase in bronchial responsiveness was demonstrated in Norwegian competitive swimmers after a heavy swimming exercise [7], and then in young ski athletes during the competitive season [8]. Inflammatory changes with lymphoid aggregates in bronchial biopsies have been demonstrated frequently in heavily trained young skiers without asthma, but with increased airways responsiveness to cold air compared to controls [9]. It seems that heavy and repeated physical endurance training over prolonged time periods, in combination with non-optimal environmental conditions, may contribute to the development of asthma among top athletes. This was first described among cross-country skiers in Norway [10] and Sweden [11, 12], and later among endurance athletes in summer sports [13] and other types of sports [2, 3]. The risk of developing asthma increases markedly when intense and frequent endurance training is combined with untoward environmental factors. HEIR and coworkers [14, 15] found that bronchial responsiveness to metacholine increased for up to 6 weeks after an upper respiratory tract infection, and also increased after training in a cold environment, as confirmed by other studies. The increased occurrence of EIB and bronchial responsiveness among elite competitive swimmers has also been connected to increased exposure to organic chloride products in indoor swimming pools. In addition, other forms of pollution have an impact upon physical performance in athletes.

Treatment of EIA in athletes

EIA is treated by pre-medication shortly before physical activity and/or by regular prophylactic anti-inflammatory treatment.

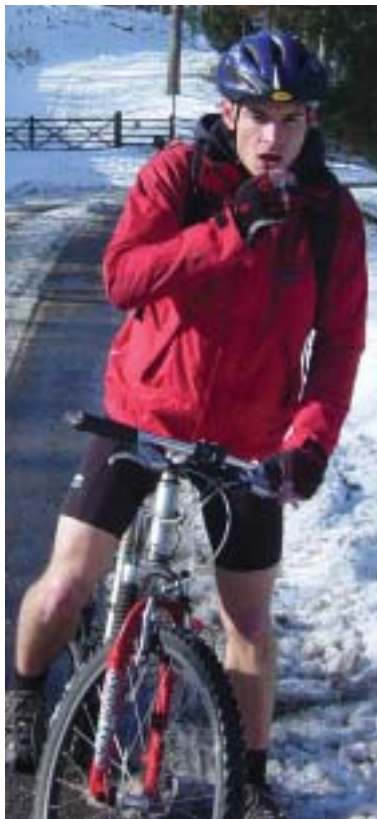
Prophylactic anti-inflammatory treatment

Anti-inflammatory treatment, especially inhaled steroids, is the most important treatment in asthma and EIA. In one study, asthmatic well-trained athletes obtained a marked reduction in EIA after a 1-week treatment with inhaled steroids, as measured by the fall in FEV₁ after a standardised treadmill run [16]. However, further treatment for 3–4 weeks was required for an improvement in peripheral bronchial obstruction [17]. Another treatment principle is the use of oral leukotrienes antagonists. There are two main groups: leukotriene synthesis antagonists and leukotriene receptor antagonists. Two days' treatment with a leukotriene synthesis inhibitor (zileuton) resulted in a protection of 40% against EIA in one study [18]. In addition, in children, the use of montelukast, a leukotriene receptor antagonist, led to a significant reduction in EIA after only 2 days' treatment both in children and adults [19, 20]. These drugs reduce EIA, and a continuous effect has been observed without development of tolerance to the drug, as has been observed during the regular use of other types of treatment. It remains to be demonstrated whether continuous use of leukotriene receptor antagonists gives an additional anti-inflammatory effect and increased improvement of EIA over time.

Disodium cromoglycate (DSCG) and nedocromil sodium have been demonstrated to improve EIA when taken before exercise. Some studies have reported an improvement of bronchial hyperresponsiveness (BHR) after the use of DSCG, whereas other studies cannot confirm this finding [21]. The most often-reported effect of DSCG and nedocromil sodium upon EIA is when taking the drugs before exercise.

Treatment before exercise

Several drugs taken before exercise protect against EIA, and the effect should be evaluated by performing an exercise test or by observing the real-life effect during training and competition. If there is no effect, treatment should be adjusted, and, especially if the diagnosis of EIA is based upon history alone, the diagnosis should be reconsidered. The most usual therapeutic drugs employed before exercise by athletes are inhaled β_2 -agonists, although DSCG and nedocromil sodium are also useful in the pre-treatment of EIA. Taken within 15 minutes before physical activity, both groups of drugs reduce the exercise-induced fall in lung function and protect against EIA for up to 2 hours after inhalation, whereas the



combination DSCG and terbutaline prolongs the protection for 4 hours. Inhaled β_2 -agonists are often preferred (in particular, the short-acting inhaled β_2 -agonists salbutamol and terbutaline) as protective treatment prior to physical activity. The protective effect against EIA is usually very good, both when bronchial constriction is present before exercise and not.

The inhaled long-acting β_2 -agonists, salmeterol and formoterol, protect effectively against EIA in combination [22]. Children with EIA will benefit from long-acting protective drugs, since they do not tend to plan their activity beforehand. In athletes performing within endurance sports, a long-acting β_2 -agonist may be of benefit as the usual β_2 -agonists may not last long enough.

Recently, the oral leukotriene antagonists have been shown to protect against EIA and experience shows them to be effective also in relation to sports. Montelukast protects for its entire therapeutic duration of 24 hours [20]. In severe EIA, practical experience shows that a beneficial additive effect may be obtained by combining several protecting drugs, such as inhaled β_2 -agonists and leukotriene antagonists.

Ipratropium bromide may be effective in protecting against EIA in singular patients. They are less useful than inhaled β_2 -agonists, but may give an additional protective effect. The optimal and individually adjusted use of asthma drugs enables asthmatic athletes to participate in competitive sports on an equal level with healthy competitors.

Relationship to doping

Frequent use of any type of drug in relation to competitive sports may cause suspicion that the drugs are used to improve physical performance and not to treat medical illness. The frequent

occurrence of EIA in participants in competitive sports has led to a high consumption of asthma drugs within these branches of athletics [10]. It has been discussed whether inhaled β_2 -agonists in particular could improve performance, especially endurance performance. In animals, it has been demonstrated that oral β_2 -agonists (clenbuterol) in high doses may cause an increase in muscle mass. This has entailed restrictions in the international doping regulations. Both inhaled steroids and inhaled β_2 -agonists are allowed for use in sports in asthmatic athletes. Systemic β_2 -agonists and systemic steroids are not allowed. From 1993, only the inhaled β_2 -agonists salbutamol and terbutaline have been permitted, but, after studies demonstrating that salbutamol, terbutaline, salmeterol and formoterol do not improve performance in sports [23], salmeterol and formoterol are now allowed for use in sports. The recently introduced oral leukotriene antagonists represent a new principle in asthma treatment and are presently allowed for use in sports. No effect has been found upon performance during cold air conditions in well-trained athletes [24].

It is the responsibility of the athlete to know the doping rules. However, the physician treating athletes should know these rules, thereby avoiding prescribing drugs not permitted for the use in sports. According to the latest regulation from the World AntiDoping Agency (WADA), both inhaled steroids and inhaled β_2 -agonists are prohibited substances, and, if used in athletes participating in international events, an application to WADA should be made prior to the participation in the sports event (www.wada-ama.org/en/t1.asp).

In conclusion, EIA is a more common occurrence in athletes than ever before. However, EIA can be controlled by a range of medications, although these have to be closely monitored in order to comply with doping regulations.

Educational questions

1. What are the main pathogenetic mechanisms causing EIA?
2. What is a frequent differential diagnosis to EIA in highly trained young people?
3. What are the most important management principles for EIA?

References

1. Ross RG. The prevalence of reversible airway obstruction in professional football players. *Med Sci Sports Exerc* 2000; 32: 1985–1989.
2. Weiler JM, Metzger J, Donnelly AL, Crowley ET, Sharath MD. Prevalence of bronchial responsiveness in highly trained athletes. *Chest* 1986; 90: 23–28.
3. Weiler JM, Layton T, Hunt M. Asthma in United States Olympic athletes who participated in the 1996 Summer Games. *J Allergy Clin Immunol* 1998; 102: 722–726.
4. Gilbert IA, McFadden ER, Jr. Airway cooling and rewarming. The second reaction sequence in exercise-induced asthma. *J Clin Invest* 1992; 90: 699–704.
5. Lee TH, Anderson SD. Heterogeneity of mechanisms in exercise-induced asthma. *Thorax* 1985; 40: 481–487.
6. Anderson SD, Daviskas E. The airway microvasculature and exercise induced asthma. *Thorax* 1992; 47: 748–752.
7. Carlsen KH, Oseid S, Odden H, Mellbye E. The response to heavy swimming exercise in children with and without bronchial asthma. In: Oseid S, Carlsen KH, eds. *Children and Exercise XIII*. Champaign, Illinois, Human Kinetics Publishers, Inc., 1989; pp. 351–360.
8. Heir T. Longitudinal variations in bronchial responsiveness in cross-country skiers and control subjects. *Scand J Med Sci Sports* 1994; 4: 134–139.
9. Sue-Chue M, Karjalainen EM, Altraja A, et al. Lymphoid aggregates in endobronchial biopsies from young elite cross-country skiers. *Am J Respir Crit Care Med* 1998; 158: 597–601.
10. Heir T, Oseid S. Self-reported asthma and exercise-induced asthma symptoms in high-level competitive cross-country skiers. *Scand J Med Sci Sports* 1994; 4: 128–133.
11. Larsson K, Ohlsen P, Larsson L, Malmberg P, Rydstrom PO, Ulriksen H. High prevalence of asthma in cross country skiers. *BMJ* 1993; 307: 1326–1329.
12. Sue-Chu M, Larsson L, Bjerner L. Prevalence of asthma in young cross-country skiers in central Scandinavia: differences between Norway and Sweden. *Respir Med* 1996; 90: 99–105.
13. Helenius JJ, Tikkanen HO, Haahtela T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. *Br J Sport Med* 1998; 32: 125–129.
14. Heir T, Aanestad G, Carlsen KH, Larsen S. Respiratory tract infection and bronchial responsiveness in elite athletes and sedentary control subjects. *Scand J Med Sci Sports* 1995; 5: 94–99.
15. Heir T, Larsen S. The influence of training intensity, airway infections and environmental conditions on seasonal variations in bronchial responsiveness in cross-country skiers. *Scand J Med Sci Sports* 1995; 5: 152–159.
16. Papalia SM. Aspects of inhaled budesonide use in asthma and exercise. Dept of Human Movement, University of Western Australia, 1996.
17. Henriksen JM, Dahl R. Effects of inhaled budesonide alone and in combination with low-dose terbutaline in children with exercise-induced asthma. *Am Rev Respir Dis* 1983; 128: 993–997.
18. Meltzer SS, Hasday JD, Cohn J, Bleecker ER. Inhibition of exercise-induced bronchospasm by zileuton: a 5-lipoxygenase inhibitor. *Am J Respir Crit Care Med* 1996; 153: 931–935.
19. Kemp JP, Dockhorn RJ, Shapiro GG, et al. Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. *J Pediatr* 1998; 133: 424–428.
20. Leff JA, Busse WW, Pearlman D, et al. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl J Med* 1998; 339: 147–152.
21. Bernard A, Carbonnelle S, Michel O, et al. Lung hyperpermeability and asthma prevalence in schoolchildren: unexpected associations with the attendance at indoor chlorinated swimming pools. *Occup Environ Med* 2003; 60: 385–394.
22. Green CP, Price JF. Prevention of exercise induced asthma by inhaled salmeterol xinafoate. *Arch Dis Child* 1992; 67: 1014–1017.
23. Carlsen KH, Hem E, Stensrud T, Held T, Herland K, Mowinkel P. Can asthma treatment in sports be doping? The effect of the rapid onset, long-acting inhaled β_2 -agonist formoterol upon endurance performance in healthy well trained athletes. *Respir Med* 2001; 95: 571–576.
24. Sue-Chu M, Sandsund M, Holand B, Bjerner L. Montelukast does not affect exercise performance at subfreezing temperature in highly trained non-asthmatic endurance athletes. *Int J Sports Med* 2000; 21: 424–428.

Suggested answers

1. Increased respiratory heat and water loss through increased ventilation caused by exercise. This may lead to reflex bronchoconstriction, mucosal oedema and mediator release in the mucous membrane.
2. Exercise-induced vocal cord dysfunction with inspiratory stridor occurring during maximal exercise load.
3. Most important is anti-inflammatory treatment, in particular with inhaled steroids, causing a rapid improvement over some weeks in EIA. It is also important to take into consideration any possible environmental hazards, like cold dry air in outdoor winter sports, or inhalation of organic chlorine compounds in indoor swimming pools.