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Review article

Exercise induced asthma in children and adolescents and the relationship to sports

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Exercise induced asthma (EIA) was described as long as 2000 years ago in Cappadocia and is a well recognised characteristic of asthma, especially in childhood and adolescence (1), indeed it is a major distinctive feature of childhood asthma, especially without anti-inflammatory treatment. It has been maintained that 70–80 per cent of untreated asthmatics suffer from EIA (2). Backer and Ulrich reported that 16 per cent of a random sample of 494 Danish children and adolescents experienced a more than ten per cent reduction in FEV_1 after a standardised exercise test (3). EIA may cause limitations in the daily life for asthmatic children, and it has been documented that many asthmatic children suffer such limitations (4, 5). It is important for children's self-esteem to participate in play and sports, therefore mastering EIA is considered an essential part of successful management of asthma (6). Furthermore, EIA may be regarded as a measure of bronchial hyperresponsiveness (7, 8), and quantifying EIA in a standardised way may help in monitoring asthma.

Pathogenesis of EIA

Presently, there are two main theories that explain the relationship between physical activity and EIA. The theory of airway cooling due to respiratory heat loss with rewarming by secondary hyperaemia and pulmonary vasodilatation will first be considered (9). As the inspiratory air is rapidly saturated with vapor during breathing, the temperature of the inspiratory air also increases. McFadden *et al.* demonstrated through thermal mapping that the temperature increased from 32.0 ± 0.05°C in the upper trachea to 35.5 ± 0.3°C in the subsegmental bronchi during quiet breathing (ventilation: 15 l/min) of room air (26.7 ± 0.5°C) (10). During increasing ventilation the temperature fell, and with a maximum ventilation of 100 to 120 l/min, the temperature in the upper trachea was 29.2 ± 0.5°C and 33.9 ± 0.8°C in the subsegmental bronchi. During maximum ventilation with frigid air (–18.6 ± 1.2°C), the upper tracheal temperature was 20.5 ± 0.6°C and the subsegmental bronchial temperature was 31.6 ± 1.2°C (10). Airway cooling may stimulate receptors in the airways, causing bronchial constriction through a reflex pathway. Furthermore, a secondary reactive hyperaemia may occur with resulting oedema and airways narrowing, due to pulmonary vasoconstriction induced by the cold air (9).

Secondly, substantial evidence indicates that exercise induced asthma is effected through the release of mediators from mast cells and other inflammatory cells of the airways (11). Increased levels of the mast cell mediator 9α,11β prostaglandin F_2 were recently found in urine after an exercise challenge in patients with EIA compared to patients without EIA, but Leukotriene E_4 (LTE_4) and N-metylhista-

mine was not found (12). However, in a study including more patients, Reiss, *et al.*, also found increased levels of LTE_4 after an exercise challenge (13). We have described signs of eosinophil and neutrophil activation (increased s-ECP and s-MPO) in top athletes after heavy training exercises, but not after moderate training exercises (14). This mediator release is the main reason for considering exercise-induced asthma as an indirect measure of bronchial reactivity (15). The release of mediators is thought to occur through several mechanisms.

The lower respiratory tract is lined by ciliary epithelium coated by pericilliary fluid. As the airways are divided into an increasing number of bronchial generations, the amount of pericilliary fluid increases exponentially (16). During breathing, respiratory vapour loss increases rapidly with increasing ventilatory rate (17). It has been debated whether the main stimulus behind the exercise-induced bronchoconstriction is water loss occurring during hyperventilation due to exercise (18) or a temperature gradient over the airways due to the respiratory heat loss (19, 20). The main factor causing the mediator release is now thought to be the change in osmolarity of the pericilliary fluid lining the surface of the respiratory mucosal membranes, whether it is caused by respiratory heat loss or 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. This is supported by the finding that inhaled furosemide, which inhibits the secretion of chloride ions into the bronchial lumen *in vitro* (21), protects against exercise-induced asthma (22). The increased extracellular osmolarity thus leads to influx into the cell particularly of Na^+ and Cl^-. Ca^{++} follows 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.

The mechanisms may be better understood by learning from findings in athletes. Mediator release from eosinophils and neutrophils increased both in healthy and asthmatic athletes after heavy exercise. S-ECP and s-MPO increased significantly two to four hours after heavy exercise, but not after moderate exercise in Norwegian Olympic cross country skiers (14). Heavy exercise may increase airway inflammation, and thus bronchial responsiveness. This increase in bronchial responsiveness has previously been demonstrated in Norwegian competitive swimmers after a heavy swimming exercise (23). Inflammatory changes with lymphoid aggregates in bronchial biopsies have also been demonstrated much more frequently in highly trained young skiers without asthma, but with increased airways responsiveness to cold air compared to control subjects (24).

EIA and late asthmatic reactions

Late allergic reactions are thought to increase airway inflammation and bronchial hyperresponsiveness (25). In a similar way, late bronchoconstrictive reactions after exercise have been described in a limited group of the children with an early bronchial reaction to exercise (26–28, 29). A relationship between late asthmatic reactions to exercise and increase in inflammatory mediators during exercise has also been described (27).

However, difficulties in reproducing the late reaction to exercise have cast doubt on the existence of a true late asthmatic reaction to exercise (30–32). It has been recommended that studies of late asthmatic reactions should be compared with control days without exercise, as late asthmatic reactions after exercise might be confused with spontaneous variation in lung function (32). Sano, *et al.*, in the present issue of *Pediatric Allergy and Immunology* report that 28.1 per cent of a group of 32 children with EIA also had a late response to exercise (within eight hours of the exercise test) (29). They compared the lung function after exercise with the spontaneous variation in lung function in the same group of children. There was a significant difference between lung function after exercise and the spontaneous variation in lung function in the same children (29). Their findings are confirmed by the recent report of Chhabra and Ojha, who demonstrate a late response to exercise in eight out of 16 patients with EIA by comparing the findings after exercise with the spontaneous variation in lung function on a control day (33).

The magnitude of EIA is determined in part by the exercise load and climatic conditions during exercise (34). By combining cold dry air inhalation and exercise, there may be a significantly greater reduction in lung function (35). This may also influence the occurrence of late asthmatic reactions after exercise. In the study of Sano, *et al.*, in the present issue of *Pediatric Allergy and Immunology*, exercise was combined with the inhalation of dry and moderately cold air (+5°C) (29). Furthermore, the use of anti-inflammatory medication (e.g. inhaled steroids) reduces the occurrence of EIA and may also influence the occurrence of late asthmatic reactions after exercise. The patients had not taken anti-inflammatory drugs the last month prior to the study. Thus, the effect of exercise load, environmental factors and use of asthma medication should also been taken into consideration in studies of this phenomenon.

Diagnosis of EIA

There are several differential diagnoses to EIA, such as exercise induced laryngeal stridor (36, 37) or hy-

perventilation. A diagnosis of EIA ought to be made before starting treatment. An exact clinical history, examination with lung function measurements before and after inhalation of a β_2-agonist, before and after a standardised exercise-test such as tread-mill run and/or a cold-air inhalation test and measurement of BHR by metacholine inhalation are parts of the diagnostic process. The extent of diagnostic procedures to be employed will vary from case to case. One important part of the diagnostic process is to follow the patient to evaluate the treatment effect.

Exercise-induced bronchoconstriction may be diagnosed in different ways, and by employing different sorts of exercise. It is important to standardise the test to compare the results of testing between different individuals and to compare results from the same individual at different times. Tests with free running, step-tests, cycling and running on a motor-driven treadmill have been standardised and used in the diagnosis of exercise-induced bronchoconstriction. Running provokes exercise-induced bronchoconstriction in children more easily than cycling, because the muscles used during running are usually better trained than the muscles used during cycling in most children. Experience has shown that running on a motor-driven treadmill is particularly useful and easy to standardise. In our laboratory, running on a motor driven treadmill with sub-maximal load is used. The treadmill has an inclination of 5.5% and during running the speed of the treadmill is gradually increased until a steady state heart rate of at least 170 beats per minute is reached. Increased sensitivity of the exercise test has been demonstrated by increasing the exercise load to a heart rate of at least 95 per cent of the calculated maximum (38). The heart rate can be measured electronically by devices such as the Sport-Tester PE 3000®. The child then runs for six minutes at this steady state. The running is performed with a room temperature of approximately 20°C and a relative humidity of approximately 40 per cent. Lung function is measured before running, immediately after the cessation of running, after 3, 6, 10, 15 and 20 minutes after running. FEV_1 is usually the lung function parameter employed and a fall of 15 per cent is most often used as a sign of exercise-induced bronchoconstriction, though some authors use a ten per cent reduction (3, 39). In addition to diagnosing EIA, the reduction in FEV_1 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. This measure of non-specific bronchial reactivity is an indirect measure (15), as it is thought to work through the release of mediators (2). It has been shown to correlate well to direct measures of bronchial reactivity, such as histamine or metacholine bronchial provocation (8). Furthermore it is a useful physiologic measure, as it reflects the effect of daily-life activities upon the asthmatic child.

Studies have shown that this test has a very high specificity for the diagnosis of asthma, but with a rather low sensitivity when compared to histamine or metacholine bronchial provocation (7, 40). When an extra stimulus is added to the exercise test, combining running on a treadmill with the inhalation of dry cold air of –20°C, the high specificity is maintained, but the sensitivity is markedly increased (35).

EIA and physical training – lessons from sport and athletes

Different types of exercise tend to provoke EIA to different degrees. Running is the type of exercise best suited to provoke EIA. Cycling, and especially swimming, perhaps due to the humid conditions during swimming, will not provoke EIA to the same extent (41). Several studies indicate that frequent heavy physical exercise may contribute to increased bronchial responsiveness. Highly trained elite athletes have been reported to have an increased incidence of asthma and EIA. Elite American football players had a very high incidence of bronchial hyperreactivity (PC_{20} metacholine) compared to volleyball players (42), and during the XXIII summer Olympic games 41 olympic medals, including 15 gold medals and 21 silver medals, were won by American athletes suffering from exercise induced bronchoconstriction (43). This high incidence of exercise induced bronchoconstriction among elite athletes raises the question whether high intensity physical training in itself may enhance bronchial reactivity. Several studies with different types of physical exercise suggest that short term exercise with a high intensity level increases bronchial reactivity (23, 44, 45). Suzuki, *et al.*, found an increase in bronchial reactivity in asthmatics after cycling (45), whereas Zawadski, *et al.*, could not confirm this. However, the latter study was performed with a moderate exercise load (46). In a previous study of elite competition swimmers in Norway, bronchial reactivity by histamine provocation (PC_{20}) was measured before and after a heavy swimming session, with three main intervals of 1000 meters swimming; the first interval five per cent below the calculated anaerobic threshold, the second interval at the calculated anaerobic threshold; and the third session at five per cent above the calculated anaerobic threshold. $PC_{20\text{-histamine}}$ was found to decrease from before to after the swimming procedure both in the asthmatic swimmers and in the non-asthmatic swimmers. The decrease in $PC_{20\text{-histamine}}$ (indicating an increase in bronchial reactivity) was significantly correlated to

the exercise load, as measured by the change in serum-lactate and base excess (23).

Exercise testing in the laboratory at a submaximal level, is not comparable to the exercise intensity which elite athletes in endurance sports employ during their training. In the predisposed individual, high intensity training for two to four hours daily for several years, may provoke airway inflammation, especially when combined with unfavourable environmental conditions such as cold air temperature or air pollution (47, 48). Norwegian studies suggest that bronchial reactivity in elite cross-country skiers increases during the most active training and competitive season (January and February), and improves when the training intensity decreases (50). Furthermore, after having trained for many years, the prevalence of asthma among the elite skiers increased markedly from approximately six per cent when the skiers were twenty years old, up to over 20 per cent when the skiers had reached the age of thirty years. This was not found in the control group (50). This suggests that heavy, long-lasting exercise may induce bronchial hyperresponsiveness in susceptible individuals. Similarly, a Swedish study reported a high prevalence of asthma among top cross-country skiers (51). It should be remembered that the physically active child and the athlete in training are more exposed to pollutants and allergens in ambient air due to hyperventilation and inhalation of larger amounts of air. It has been demonstrated that in indoor pools, swimmers may be exposed to levels of chlorine at the limit of maximum allowable levels in industry (52). In summer sports, an increased prevalence of asthma was found among long distance runners. They also had more frequent allergy to seasonal allergens such as birch and grass pollen (53). Thus, a combination of endurance training and an environmental hazard such as cold air, seasonal allergens, pollutants or respiratory virus infections tend to increase the occurrence of asthma among athletes.

Management of EIA

General therapeutic measures

Environmental measures, efforts related to training, as well as drug treatment, belong to the treatment strategies. Physical warming-up is among the general efforts related to training procedures. This is an important way of preventing EIA. Protection against cold air inhalation is also important. Different equipment may be used, employing the heat exchange principle. The expired air of 37°C is employed to warm up the inspired air. Jonaset®, Jonaset Sport® and Lungplus® are in common use. In order to protect the athlete against developing BHR, they should not perform endurance training or participate in competition while suffering viral respiratory infections or in cold air. Furthermore, intense physical activity in polluted air should be avoided.

Drug treatment of exercise induced asthma

The drug treatment of EIA consists of pre-medication shortly before physical activity or training and prophylactic treatment. Prophylaxis consists mainly of anti-inflammatory treatment. Furthermore, symptoms occurring through exercise must also be treated.

Prophylactic anti-inflammatory treatment.
In order to master physical activity, the asthmatic disorder should be treated optimally to improve bronchial hyperresponsiveness and to maintain control of the disease activity. The usual guidelines for treating asthma should be followed. Anti-inflammatory treatment is presently the cornerstone in treating asthma, and is also crucial in order to master EIA. Inhaled steroids are the most important treatment. Already after one week's treatment with inhaled steroids (budesonide) in asthmatic well-trained athletes, a marked reduction in EIA was observed, as measured by the fall in FEV_1 after a standardised tread mill run (54). The same was observed in asthmatic children as far back as 15 years ago, but in order to obtain a significant reduction of MEF_{25-75}, a measure of peripheral bronchial obstruction, further treatment of three to four weeks was necessary (55). It is also demonstrated that a more rapid effect from inhaled steroids is observed upon EIA than upon BHR as measured by metacholine bronchial provocation. The anticipated improvement of EIA is reached after two to three months treatment with inhaled steroids (39). On the other hand, improvement of BHR as measured by metacholine provocation has been observed for up to 22 months (56).

Another treatment principle, which is presently being introduced, is the use of leukotriene antagonists, taken orally. There are two main groups of leukotriene antagonists, leukotriene synthesis antagonists and leukotriene receptor antagonists. These drugs may reduce EIA, but further experience is needed before these drugs may be used routinely. After a single dose, leukotriene antagonists are significantly better than placebo against EIA (57), and two days treatment with a leukotriene anatagonist (zileuton) caused a protection of 40% against EIA (58).

The other anti-inflammatory asthma drugs, which have been used for many years, are disodium cromoglycate (DSCG), and the related, more recently introduced nedocromil sodium. Some studies report

an improvement of BHR after the use of DSCG, whereas other studies cannot confirm this finding (59, 60). The most often reported benefit of DSCG and nedocromil sodium upon EIA, is when taking the drugs before exercise (61).

Treatment before exercise

A number of different drugs may be taken before exercise to protect against EIA. The effect of all these drugs should be evaluated by performing an exercise test or by a follow-up consultation. If no benefit is observed, the treatment should be adjusted or, especially if the diagnosis of EIA is based upon history alone, the diagnosis should be reconsidered. The most common therapeutic drugs employed before exercise are inhaled $ß_2$-agonists, DSCG or nedocromil sodium and, more rarely, inhaled ipratropium bromide (62).

Both DSCG and nedocromil sodium have been demonstrated to be useful in the pre-treatment of EIA (62–64). Taken within 15 minutes before physical activity, they reduce the lung function decrease provoked by the activity. It has been demonstrated that DSCG, in addition to protecting against EIA, also reduces ventilation and energy consumption during running. Maximum oxygen uptake was significantly lower when the children inhaled DSCG or the $ß_2$-agonist salbutamol before physical activity when compared to placebo (65). It has also been shown that DSCG reduces the ventilatory work in children suffering from EIA, but not in healthy children (66). This suggests that the energy consumption during exercise is higher in untreated than in treated asthmatic children and that pre-treatment with DSCG or an inhaled $ß_2$-agonist enables asthmatic children, adolescents and athletes to participate in sports and physical activity on an equal level with healthy children, adolescents and athletes.

Both DSCG and the inhaled $ß_2$-agonist terbutaline have been found to protect against EIA for up to two hours after inhalation, whereas the combination of DSCG and terbutaline protected for four hours. Thus, combining the two drugs prolonged the protection (67). It has been maintained that an inhaled $ß_2$-agonist is preferable when there is baseline bronchial constriction, whereas DSCG should be used when the subject does not demonstrate signs of bronchial constriction prior to the physical activity (62). It is important that DSCG is taken in adequate doses; 20 mg is to be preferred. This sometimes makes treatment impractical, and inhaled $ß_2$-agonists are often preferred.

The protective effect of inhaled $ß_2$-agonists against EIA is usually very good, both when bronchial constriction is present before exercise and when it is not (62). The short-acting inhaled $ß_2$-agonists, salbutamol and terbutaline are usually preferred. Inhaled $ß_2$-agonists have a better effect than when the drugs are taken orally. The recommended dose of inhaled salbutamol is 0.2 to 0.4 mg, corresponding to an inhaled dose of 0.25 to 0.5 mg terbutaline.

Long-acting $ß_2$-agonists for inhalation, salmeterol and formoterol have recently been introduced. Both have been demonstrated to have good protective effects against EIA (68–70). Children with EIA will benefit from a long-acting protective drug as they do not plan their activity beforehand. In athletes performing endurance sports, a long-acting $ß_2$-agonist may be of benefit as the usual $ß_2$-agonists may not last long enough. In addition, the use of a long-acting $ß_2$-agonist may improve symptom control and quality of life both in the asthmatic athlete and in asthmatic children and adolescents (71, 72).

Ipratropium bromide may be effective in protecting against EIA in some singular patients, but are less useful than inhaled $ß_2$-agonists (62, 73). However, in certain subjects ipratropium bromide should be tried. Sometimes an additional protective effect may be obtained when ipratropium bromide is added to an inhaled $ß_2$-agonist (74). This underlines the importance of trying out the effect of the prescribed drugs.

Lately a protective effect of inhaled furosemide (22) and inhaled heparin (75) upon EIA has been described. This is of considerable theoretical interest, but these drugs currently do not represent a therapeutic alternative to the other treatments.

The latest group of drugs reported to have an effect upon EIA are leukotriene antagonists (13, 57, 58). The magnitude of EIA is reduced, but not completely abolished (76).

The relationship to doping

The frequent occurrence of EIA in participants in endurance sports has led to a high consumption of asthma drugs within these branches of athletics (50, 51). Thus, it has been discussed whether inhaled $ß_2$-agonists in particular could improve performance, especially for endurance athletes. In animals it has been demonstrated that the oral $ß_2$-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 $ß_2$-agonists are allowed for use in sports in asthmatic athletes. Systemic $ß_2$-agonists and systemic steroids are not allowed. From 1993, only the inhaled $ß_2$-agonists salbutamol and terbutaline were allowed for asthmatics for use in sports, but after studies demonstrating that salbutamol, terbutaline and salmeterol do not improve performance in sports (77–80), salmeterol was allowed for use in sports after 1 February, 1996.

Conclusions

The asthmatic condition should be treated optimally in athletes and children suffering from EIA. This usually includes the use of inhaled steroids, which reduces BHR and EIA considerably. However, additional protective medication before exercise is often needed. Inhaled $ß_2$-agonists, usually short-acting, are most often used. EIA is usually well mastered by combining inhaled steroids and inhaled $ß_2$-agonists. Long-acting inhaled $ß_2$-agonists may be necessary, especially in severe asthma, but also in children, who do not plan their physical activity in the same way as athletes. The use of asthma drugs is restricted within sports and the athlete has a responsibility to know the doping rules. However, the physician should also know these rules, thereby avoiding the prescription of banned drugs. For the individual patients and the individual athlete it is important that the effectiveness of the prescribed treatment is reassessed.

In addition to medical treatment, certain preventive measures should be ensured in order to help the athlete avoid the dangers of heavy endurance training and competition. Endurance training and competition should not be performed during a respiratory tract infection, nor in cold temperatures (below – 10°C) without cold-protection equipment. In indoor swimming pools, adequate ventilation should be ensured in order not to expose the swimmers to high levels of chlorine in inhaled air.

Asthmatic children and participation in sports

What are the prospects for asthmatic children? On the one hand, participation in physical activity, play and sport is important for the asthmatic child, but the asthmatic child should learn to take certain precautions, such as avoiding physical activity in ambient cold air and ambient pollution. Rather than avoiding physical activity and sport, care should be taken to help the asthmatic child to participate together with others in sport, because mastering sport and physical activity is a good measure of mastering asthma. The physician treating children and adolescents with EIA, should have a good knowledge about the doping rules and prescribe drugs that are allowed for use in sport.

References

1. ADAMS F. The extant works of Aretaeus, the Cappodician. London: The Sydenham Society 1856: 316.
2. LEE TH, ANDERSON SD. Heterogeneity of mechanisms in exercise-induced asthma. Thorax 1985: 40: 481–7.
3. BACKER V, ULRIK CS. Bronchial responsiveness to exercise in a random sample of 494 children and adolescents from Copenhagen. Clin Exp Allergy 1992: 22: 741–7.
4. TAYLOR WR, NEWACHECK PW. Impact of childhood asthma upon health. Pediatrics 1992: 90: 657–62.
5. LENNEY W, WELL NEJ, O'NEILL BA. The burden of paediatric asthma. Eur Respir Rev 1994: 4: 49–62.
6. International Paediatric Consensus Group on Asthma. Asthma: a follow up statement from an international paediatric asthma consensus group. Arch Dis Child 1992: 67: 240–8.
7. GODFREY S, SPRINGER C, NOVISKI N, MAAYAN CH, AVITAL A. Exercise but not metacholine differentiates asthma from chronic lung disease in children. Thorax 1991: 46: 488–92.
8. CARLSEN KH, BECH R, OSEID S, et al. Bronchial reactivity measured by exercise-induced asthma test and PC-20-histamine: A comparison of two methods. In: MOREHOUSE CA, ed. Children and Exercise XII. Champaign, Illinois: Human Kinetics 1986: p. 295–300.
9. GILBERT IA, MCFADDEN JR ER. Airway cooling and rewarming. The second reaction sequence in exercise-induced asthma. J Clin Invest 1992: 90: 699–704.
10. MCFADDEN JR ER, PICHURKO BM, BOWMAN HF, et al. Thermal mapping of the airways in humans. J Appl Physiol 1985: 58: 564–70.
11. LEE TH, NAGAKURA T, PAPAGEORGIOU N, CROMWELL O, IKURA Y, KAY AB. Mediators in exercise-induced asthma. J Allergy Clin Immunol 1994: 73: 634–9.
12. O'SULLIVAN S, ROOQUET A, DAHLÉN B, et al. Evidence for mast cell activation during exercise-induced bronchoconstriction. Eur Respir J 1998: 12: 345–50.
13. REISS TF, HILL JB, HARMAN E, et al. Increased urinary excretion of LTE4 after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist. Thorax 1997: 52: 1030–5.
14. RØNSEN O, HEM E, EDVARDSEN E, HALVORSEN R, CARLSEN KH. Changes in airways inflammatory markers during high intensity training in elite cross country skiers. Eur Respir J 1995: 8: 473.
15. PAUWELS R, JOOS G, VAN DER STRATEN M. Bronchial responsiveness is not bronchial responsiveness is not asthma. Clin Allergy 1988: 18: 317–21.
16. ANDERSON SD. Exercise-induced asthma: Stimulus, mechanism and management. In: BARNES PJ, ROGER IW, THOMSON NC, eds. Asthma. Basic mechanisms and clinical management. London: Academic Press 1988. p. 503–22.
17. ANDERSON SD, SCHOEFFEL RE, BLACK JL, DAVISKAS E. Airway cooling as the stimulus to exercise-induced asthma. A re-evaluation. Eur Respir J 1985: 67: 20–30.
18. SHEPPARD D, ESCHENBACHER WL. Respiratory water loss as a stimulus to exercise-induced bronchoconstriction. J Allergy Clin Immunol 1984: 73: 640–2.
19. ANDERSON SD, DAVISKAS E. The airway microvasculature and exercise induced asthma. Thorax 1992: 47: 748–52.
20. LEE TH, ASSOUFI BK, KAY AB. The link between exercise, respiratory heat exchange, and the mast cell in bronchial asthma. Lancet 1983; i: 520–2.
21. WIDDICOMBE JH, NATHANSON IT, HIGHLAND E. Effects of "loop" diuretics on ion transport by dog tracheal epithelium. Am J Physiol 1983: 245: 388–396.
22. BIANCO S, VAGHI A, ROBUSCHI M, PASARGIKLIAN M. Prevention of exercise-induced bronchoconstriction by inhaled frusemide. Lancet 1988: 2: 252–5.
23. CARLSEN KH, OSEID S, ODDEN H, et al. 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 1989: p. 351–60.
24. 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.
25. COCKCROFT DW, RUFFIN RE, DOLOVICH J, HARGREAVE FE. Allergen-induced increase in non-allergic bronchial reactivity. Clin Allergy 1977: 7: 503–13.
26. BIERMAN CW, SPIRO SG, PETHERAN DJ. Late response in exercise-induced asthma. J Allergy Clin Immunol 1980: 65: 206.
27. LEE TH, NAGAKURA T, PAPAGEORGIOU N, et al. Exercise-induced late asthmatic reactions with neutrophil chemotactic activity. N Engl J Med 1983: 308: 1502–5.
28. BONER AL, NIERO E, ANTOLINI I, WARNER JO. Biphasic (early and late) asthmatic responses to exercise in children with severe asthma, resident at high altitude. Eur J Pediatr 1985: 144: 164–6.
29. SANO F, SOLE D, NASPITZ CK. Prevalence and characteristics of exercise-induced asthma. Pediatr Allergy Immunol 1998. Ped Allergy Immunol 1998: 9: 181–5.
30. BONER AL, VALLONE G, CHIESA M, SPEZIA E, FAMBRI L, SETTE L. Reproducibility of late phase pulmonary response to exercise and its relationship to bronchial hyperreactivity in children with chronic asthma. Pediatr Pulmonol 1992: 14: 156–9.
31. HOFSTRA WB, STERK PJ, NEIJENS HJ, KOUWENBERG JM, MULDER PG, DUIVERMAN EJ. Occurrence of a late response to exercise in asthmatic children: multiple regression approach using time-matched baseline and histamine control days. Eur Respir J 1996: 9: 1348–55.
32. PERONI DG, BONER AL. Exercise-induced asthma: Is there space for late-phase reactions? Eur Respir J 1996: 9: 1335–8.
33. CHHABRA SK, OJHA UC. Late asthmatic response in exercise-induced asthma. Ann Allergy Asthma Immunol 1998: 80: 323–7.
34. NOVISKI N, BAR-YISHAY E, GODFREY S. Exercise intensity determines and climatic conditions modify the severity of exercise-induced asthma. Am Rev Respir Dis 1987: 136: 592–4.
35. CARLSEN KH, ENGH G, MØRK M, SCHRØDER E. Cold air inhalation and exercise-induced bronchoconstriction in relationship to metacholine bronchial responsiveness. Different patterns in asthmatic children and children with other chronic lung diseases. Respir Med 1998: 92: 308–15.
36. LANDWEHR LP, WOOD RP, BLAGER FB, MILGROM H. Vocal cord dysfunction mimicking exercise-induced bronchospasm in adolescents. Pediatrics 1996: 98: 971–4.
37. MCFADDEN JR ER, ZAWADSKI DK. Vocal cord dysfunction masquerading as exercise-induced asthma. A physiologic cause for "choking" during athletic activities. Am J Respir Crit Care Med 1996: 153: 942–7.
38. ENGH G, MØRK M, CARLSEN KH. Exercise induced bronchoconstriction depends on exercise load. Am J Respir Crit Care Med 1998: 157: A621
39. WAALKENS HJ, VAN ESSEN-ZANDVLIET EE, GERRITSEN J, DUIVERMAN EJKK, KNOL K. The effect of an inhaled corticosteroid (budesonide) on exercise-induced asthma in children. Dutch CNSLD Study Group. Eur Respir J 1993: 6: 652–6.
40. AVITAL A, SPRINGER C, BAR YISHAY E, GODFREY S. Adenosine, methacholine, and exercise challenges in children with asthma or paediatric chronic obstructive pulmonary disease. Thorax 1995: 50: 511–6.
41. BAR-OR O, INBAR O. Swimming and asthma. Benefits and deleterious effects. Sport Med 1992: 14: 397–405.
42. WEILER JM, METZGER J, DONNELLY AL, CROWLEY ET, SHARATH MD. Prevalence of bronchial responsiveness in highly trained athletes. Chest 1986: 90: 23–8.
43. PIERSON WE. Exercise-induced bronchospasm in the XXIII summer olympic games. N Engl Reg Allergy Proc 1988: 9: 209–13.
44. MAGNUSSEN H, REUSS G, JÖRRES R. Airway response to metacholine during exercise induced refractoriness in asthma. Thorax 1986: 41: 667–670.
45. SUZUKI S, CHONAN T, SASAKI H, et al. Bronchial hyperresponiveness to metacholine after exercise in asthmatics. Ann Allergy 1985: 54: 136–141.
46. ZAWADSKI DK, LENNER KA, MCFADDEN JR ER. Effect of exercise on nonspecific airway reactivity in asthmatics. J Appl Physiol 1988: 64: 812–6.
47. MAHLER DA, LOKE J. Lung function after marathon running at warm and cold ambient temperatures. Am Rev Respir Dis 1981: 124: 154–7.
48. ADAMS WC. Effects of ozone exposure at ambient air pollution epidsode levels on exercise performance. Sport Med 1987: 4: 395–424.
49. HEIR T, LARSEN S. The influence of training intensity, airway infections and evironmental conditions on seasonal variations in bronchial responsiveness in cross-country skiers. Scand. J Med Sci Sports 1995: 5: 152–9.
50. 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: 128–33.
51. LARSSON K, OHLSEN P, LARSSON L, MALMBERG P, RYDSTROM PO, ULRIKSEN H. High prevalence of asthma in cross country skiers. BMJ 1993: 307: 1326–9.
52. DROBNIC F, FREIXA A, CASAN P, SANCHIS J, GUARDINO X. Assessment of chlorine exposure in swimmers during training. Med Sci Sports Exerc 1996: 28: 271–4.
53. HELENIUS IJ, TIKKANEN HO, HAAHTELA T. Association between type of training and risk of asthma in elite athletes. Thorax 1997: 52: 157–60.
54. PAPALIA, SM. Aspects of inhaled budesonide use in asthma and exercise. Department of Human Movement, University of Western Australia 1996.
55. 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: 993–7.
56. VAN ESSEN-ZANDVLIET EE, HUGHES MD, WAALKENS HJ, et al. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2 agonists on lung function, airway responsiveness, and symptoms in children with asthma. Am Rev Respir Dis 1992: 146: 547–54.
57. ROBUSCHI M, RIVA E, FUCCELLA LM, et al. Prevention of exercise-induced bronchoconstriction by a new leukotriene antagonist (SK&F 104353). A double-blind study versus disodium cromoglycate and placebo. Am Rev Respir Dis 1992: 145: 1285–8.
58. 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: 931–5.
59. HOAG JE, MCFADDEN JR ER. Long-term effect of cromolyn sodium on nonspecific bronchial hyperresponsiveness: a review. Ann Allergy 1991: 66: 53–63.
60. CARLSEN KH, LARSSON K. The efficacy of inhaled disodium cromoglycate and glucocorticoids. Clin Exp Allergy 1996: 26 Suppl 4: 8–17.
61. BENEDICTIS FM, TUTERI G, BERTOTTO A, BRUNI L, VACCARO R. Comparison of the protective effects of cromolyn sodium and nedocromil sodium in the treatment of exercise-induced asthma in children. J Allergy Clin Immunol. 1994: 94: 684–8.
62. ANDERSON SD. Drugs and the control of exercise-induced asthma. Eur Respir J 1993: 6: 1090–2.

63. COMIS A, VALLETTA EA, SETTE L, ANDREOLI A, BONER AL. Comparison of nedocromil sodium and sodium cromoglycate administered by pressurized aerosol, with and without a spacer device in exercise-induced asthma in children. Eur Respir J 1993: 6: 523–6.
64. OSEID S, MELLBYE E, HEM E. Effect of nedocromil sodium on exercise-induced bronchoconstriction exacerbated by inhalation of cold air. Scand. J Med Sci Sports 1995: 5: 88–93.
65. ZANCONATO S, BARALDI E, SANTUZ P, MAGAGNIN G, ZACCHELLO F. Effect of inhaled disodium cromoglycate and albuterol on energy cost of running in asthmatic children. Pediatr Pulmonol 1990: 8: 240–4.
66. BARALDI E, SANTUZ P, MAGAGNIN G, FILIPPONE M, ZACCHELLO F. Effect of disodium cromoglycate on ventilation and gas exchange during exercise in asthmatic children with a postexertion FEV_1 fall less than 15 percent. Chest 1994: 106: 1083–8.
67. WOOLLEY M, ANDERSON SD, QUIGLEY BM. Duration of protective effect of terbutaline sulfate and cromolyn sodium alone and in combination on exercise-induced asthma. Chest 1990: 97: 39–45.
68. GREEN CP, PRICE JF. Prevention of exercise induced asthma by inhaled salmeterol xinafoate. Arch Dis Child 1992: 67: 1014–7.
69. CARLSEN KH, RØKSUND O, OLSHOLT K, NJÅ F, LEEGAARD J, BRATTEN G. Overnight protection by inhaled salmeterol on exercise-induced asthma in children. Eur Respir J 1995: 8: 1852–5.
70. BONER AL, SPEZIA E, PIOVESAN P, CHIOCCA E, MAIOCCHI G. Inhaled formoterol in the prevention of exercise-induced bronchoconstriction in asthmatic children. Am J Respir Crit Care Med 1994: 149: 935–9.
71. STEFFENSEN I, FAURSCHOU P, RISKA H, ROSTRUP J, WEGENER T. Inhaled formoterol dry powder in the treatment of patients with reversible obstructive airway disease. A 3-month, placebo-controlled comparison of the efficacy and safety of formoterol and salbutamol, followed by a 12-month trial with formoterol. Allergy 1995: 50: 657–63.
72. JUNIPER EF, JOHNSTON PR, BORKHOFF CM, GUYATT GH, BOULET LP, HAUKIOJA A. Quality of life in asthma clinical trials: comparison of salmeterol and salbutamol. Am. J Respir Crit Care Med 1995: 151: 66–70.
73. FINNERTY JP, HOLGATE ST. The contribution of histamine release and vagal reflexes, alone and in combination, to ex ercise-induced asthma. Eur Respir J 1993: 6: 1132–7.
74. GREENOUGH A, YUKSEL B, EVERETT L, PRICE JF. Inhaled ipratropium bromide and terbutaline in asthmatic children. Respir Med 1993: 87: 111–4.
75. GARRIGO J, DANTA I, AHMED T. Time course of the protective effect of inhaled heparin on exercise-induced asthma. Am J Respir Crit Care Med 1996: 153: 1702–7.
76. 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: 147–52.
77. MEEUWISSE WH, MCKENZIE DC, HOPKINS S, ROAD JD, HOPKINS SR. The effect of salbutamol on performance in nonasthmatic athletes. Med Sci Sports Exerc 1992: 24: 1161–6.
78. MORTON AR, PAPALIA SM, FITCH KD. Is salbutamol ergogenic?: The effects of salbutamol on physical performance in the high-performance nonasthmatic athletes. Clin J Sport Med 1992: 2: 93–7.
79. CARLSEN KH, INGJER F, THYNESS B, KIRKEGAARD H. The effect of inhaled salbutamol and salmeterol on lung function and endurance performance in healthy well-trained athletes. Scand J Med Sci Sports 1997: 7: 160–5.
80. HEIR T, STEMSHAUG H. Sabutamol and high-intensity treadmill running in nonasthmatic highly conditioned athletes. Scand J Med Sci Sports 1995: 5: 231–6.