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Sports in extreme conditions

The impact of exercise in cold temperatures on asthma and bronchial hyperresponsiveness in athletes

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Introduction

Outdoor cold air exposure is a frequent occurrence in many types of sports. In outdoor winter sports sub-freeze temperatures are often preferred. In several winter sports respiratory problems have frequently been reported and in particular exercise induced asthma (EIA) and bronchial hyperresponsiveness (BHR). However, the realisation of the frequent occurrence of asthma among athletes came gradually. From the early 1990ties several reports on asthma and BHR were made in cold weather athletes. The first report on increased occurrence of BHR was made by Larsson in 1993 on Swedish cross country skiers (1), and then by Heir in Norwegian competitive cross country skiers, who reported increasing prevalence with increasing age and increasing number of competitive years (2). From studies on young military skiers Heir also reported that respiratory virus infections led to prolonged periods of increased bronchial responsiveness (3) . Of particular interest was the finding that exercise intensity level above 90% of maximum heart level accounted for 54% of the variation in BHR, and that the level of BHR was highest after the coldest part of the year (4). On the other hand, Sue-Chu et al found somewhat contradictory a high frequency of asthma and BHR in Swedish skiers, but not so high in young Norwegian skiers: A clinical diagnosis of asthma was made in 42% of Swedish cross-country skiers compared to 12% in young Norwegian cross-country skiers, whereas the frequency of BHR to metacholine was 43% in Swedish skiers compared to 14% in the Norwegian skiers (5).

Among all athletes in the American winter Olympic team, 1998, Wilber et al found exercise-induced bronchoconstriction (EIB = reduction in FEV1 ≥10%) after a field exercise test (competition or simulated competition) in 23%, compared to 50% in the cross-country skiers (6), later confirmed by Rundell et al (7). Investigating applications for the use of inhaled asthma drugs, Ken Fitch found that endurance winter sports and especially cross-country skiing (17.2%) accounted for most of the approved applications in the 2002, 2006 and 2010 winter Olympic Games (8). Exercised induced asthma (EIA) and exercised induced bronchoconstriction (EIB) have been used interchangeably, but a Task Force of European Respiratory Society and European Academy of Allergy and Clinical Immunology defined EIA as symptoms and signs of asthma developing after physical exercise, whereas EIB was defined as the reduction in lung function (FEV_1) occurring after e standardised exercise test (9).

Also for other winter sports than cross country skiing reports on increased prevalence of asthma and BHR has been made, including biathlon and Nordic combined (10), figure skaters (11, 12). ice hockey players (13, 14) and speed skaters (10). Of all illnesses reported during the Winter Olympics 2010, 62.8% were respiratory illnesses (15).

Based upon these reports, how can we explain the reported increased prevalence of asthma and BHR among elite winter endurance athletes, and can we use available scientific evidence to take primary and secondary preventive measures to prevent asthma development in elite endurance athletes and in those athletes affected, how to treat to reduce symptoms and to prevent long-lasting harm from the sports activities?

The aim of the present review article is to assess available evidence of pathogenic mechanisms and cold air inhalation and to present measures and treatment, which may prevent the development of asthma and BHR in these susceptible athletes.

Mechanisms of Exercise induced asthma and Cold Air

R.S. Jones was the first to publish scientific works on EIA exactly 50 and 51 years ago (16, 17). Two main theories have been presented and debated as to what causes EIA (18-22). The first theory launched related to loss of heat and cooling of the airways due to the increased ventilation rate during exercise (23). Through the respiration the inhaled air is warmed up to 37°C and is fully saturated with vapour. The respiratory heat loss increases with increasing exercise intensity due to increased ventilation. The respiratory heat loss and cooling of the airways will further be enhanced if the inhaled air is cold (24, 25). The cooled airways result in reflex parasympathetic nerve stimulation causing bronchoconstriction, and at first reflex vasoconstriction of bronchial venules to conserve heat. At cessation of exercise, the increased ventilation ceases, and so do the cooling stimulus, causing a rebound vasodilatation. The resulting smooth muscle constriction due to nerve stimulation and mucosal oedema due to vasodilatation in susceptible individuals (26), reduces the size of the bronchial lumen with increased airways resistance (27).

The other theory is based upon that the enhanced water loss due to the increased minute ventilation increases the osmolality in the extracellular fluid of the bronchial mucosal membranes. This further induces an efflux of intracellular water to the extracellular space (28) causing an intracellular increase in ion concentration (29). This process result in release of mediators; both newly formed eicosanoids (30) and preformed mediators like histamine from intracellular granules are released and cause bronchoconstriction. In addition to

its cooling effect cold air much less water than air at higher temperatures such as room temperatures (Figure 1). The exhaled air warmed up to 37°C will contain much more water than inhaled cold air of -20°C, thus greatly enhancing also the water loss (28).

Mechanisms of Athlete's Asthma and Cold Air

That EIA might represent a specific problem in sports medicine was not realised until 1989 (31). 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 correlated with the increase in exercise load (increase in blood lactate) in both asthmatic and healthy swimmers (31). Several reports followed on cold weather types of endurance sports like cross-country skiing and the frequent occurrence of asthma and BHR among the elite athletes (1, 2), and when seasonal variation in BHR was examined in young military ski recruit troop, it was found that BHR to metacholine was most pronounced just after the coldest period of the year (4). 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 (32).

Also in exercising animals inflammatory changes in the airways have been found. In particular, epithelial damage is a repeated finding. Mice, exercised by running, developed inflammation and epithelial damage in their airways as compared to sedentary mice (33). Also in Alaskan sledge dogs exposed both to cold air and to

strenuous exercise over several days and examined by bronchoscopy with bronchoalveolar lavage (BAL) before and after a sledge race across Alaska epitheial debris and inflammatory changes were found in the BAL fluid (34). The epithelial damage and reduced repair were also found to be of major importance in experimental studies (35), suggesting this to be the primary lesion in asthma and EIB. The primary lesion may be epithelial damage due to the heavily increased ventilation during the intensive exercise with the exposure to cold air increasing water-loss and causing increased parasympathetic nervous activity, increased bronchial smooth muscle contraction, increased bronchial mucus production and increased airways inflammation leading to BHR and asthma symptoms (Figure 2). During normal tidal breathing, the nose functions like a rebreathing organ with warming up and humidifying the inspired air. As the exercise increases, the demands for ventilation increases, and the athletes will stop breathing trough the nose and instead have oral ventilation. This will further increase the heat and water loss through the expired air.

This hypothesis is supported by the following findings:

Positive metacholine bronchial challenges were found more often in competitive swimmers and winter sport athletes compared to healthy controls (36). Positive tests for eucapnic voluntary hyperpnoea were found in comparable numbers (37). Inflammatory markers in induced sputum with increased neutrophil cell counts in induced sputum were found both in swimmers and winter sport athletes, and the neutrophil counts correlated to number of training hours per week in both groups (36). Eosinophil counts were increased in swimmers in particular, as also was number of bronchial epithelial cells (36).

Also amateur endurance runners had increased number of bronchial epithelial cells with apoptosis in induced sputum after repeated half-marathon races, in addition to increased serum levels of clara cell protein 16 (CC 16) and increased supernatant interleukin 8 levels in induced sputum (38). Also after exercise testing urinary levels of CC16 increased, but the levels were reduced when the study subjects inhaled warm, humid air during running (39), whereas urinary CC 16 levels were increased after performing eucapnic voluntary hyperpnoea test with dry air, whether they had a positive test with bronchial constriction or not (40). This can be taken as a sign of lung epithelial stress after exercise causing bronchial constriction. Similarly increased levels of urinary CC 16 levels was found after exercise test in swimmers, but not after mannitol test. Again increased CC16 levels was found after exercise tests both with positive and negative responses (41). Furthermore, Hallstrand found increased number of columnar epithelial cells in induced sputum of asthmatic patients with EIB, compared to asthmatic patients without EIB (42), and also reported increased expression of the gel-forming mucin, MUC5AC measured by polymerase chain reaction in induced sputum. Also the levels of supernatant cystienyl leukotrienes, and the ratio of cysteinyl leukotrienes to prostaglandins were higher in patients with EIB (42). Furthermore, the number of columnar epithelial cells were related to degree of EIB and associated with the supernatant sputum levels of cysteinyl leukotrienes and histamine (43). These findings indicate epithelial damage in the respiratory mucous membranes with mucin hyperproduction and a link from epithelial damage to increased airways inflammation through the presence of increased levels of cysteinyl leukotrienes

and histamine in induced sputum as well as increased expression of MUC5AC (43).

The link between respiratory epithelial damage and increased airways inflammation is further strengthened by the findings that epithelial damage in asthma is linked to increased secretion of IL 17 and IL 22, and that IL-17 and IL-22 production by Th17 cells plays a critical role in established asthma (44).

Extracellular water movement across cell membranes is an important mechanistic part of the pathogenesis of EIA (28). Aquaporin is a channel for aqueous water transport driven by osmotic forces generated by sodium and chlorine ions and expressed in respiratory sub epithelial glandular cells and alveolar type 1 cells of the lungs (45). Mice lacking the gene for the aqueous water channel aquaporin (Aqp) 5 exhibit methacholine-induced bronchiolar hyperresponsiveness in comparison with normal mice (46). Park et al found a relationship between metacholine bronchial responsiveness and diminished pilocarpine induced sweat secretion, tearing rate and salivary flow rate in healthy athletes (45) indicating an autonomic dysfunction with involvement of the parasympathetic nervous system.

Intensive and regularly repeated training influences autonomic regulation. Filipe et al demonstrated increased parasympathetic activity in athletes, especially in endurance runners by pupillometry (47). Also Knopfli et al in two studies reported higher parasympathetic nervous activity in top cross-country skiers and in training children using an 4 seconds exercise test and influence upon R-R distance in electrocardiogram (48, 49). In addition there is increased parasympatethic tone in exercise induced bronchoconstriction (EIB) as shown by the blocking effect of atropine inhalation on EIB induced by cold air inhalation (50).

The training environment is important for the adolescent athlete. Due to regular exercise up to twice daily with increased minute ventilation especially when training endurance, the athlete has a higher exposure to environmental air and possible pollutants and chemicals in the surrounding air.

As stated, young competitive swimmers develop BHR at an earlier age, earlier than competitive cross-country skiers (51, 52). Exposure for swimming pools has been reported to increase asthma prevalence and exercise induced asthma in Belgian children (53), even though a large English birth cohort study contradicted this finding and found cumulative swimming to be associated with increased lung function and decreased risk of asthma symptoms, especially in children with pre-existing respiratory illness (54). Several studies have reported increased neutrophils and eosinophils in induced sputum from competitive swimmers (55, 56) and frequently bronchial hyperresponsiveness (51, 55, 56). Recently, similar findings as previously reported in bronchial biopsies from cross-country skiers (32) was found in swimmers (57).

Increased LTB_4 levels in exhaled breath condensate was reported in Italian elite swimmers (58). The environmental agent active in swimming pools is organic chlorine products, thought to cause airways inflammation and bronchial hyperresponsiveness (59)

Different types of sport will have different environmental exposures. Cross country skiers are repeatedly exposed to cold air (2), athletes training and competing in ice rinks may be exposed to NOx from the freezing machinery as well as to ultrafine particles from the resurfacing machines (60), in line with reports of high asthma prevalence among ice-hockey players (14) and figure skaters (11).

A study from South-California including 3535 children living in six areas with a high pollution levels (ozone) and six with low pollution levels, reported after a five year follow-up that children actively participating in more than three types of sports in areas with high ozone levels had an increased risk of asthma. Participating in sports in areas with low ozone levels gave no increased risk of asthma (61). The mechanisms and factors working together in developing asthma in elite athletes have been summarised in Figure 2.

Whereas the initial stimulus to this process most probably is given by the markedly increased ventilation due to repeated intensive training sessions and repeated competitions, cold air contribute by stimulating the parasympathetic nervous system, thereby increasing contraction of bronchial smooth muscle and increasing inflammation through generation of mediators like cysteinyl leukotrienes and inducing mucus hypersecretion. When also other stimuli contribute to this process by causing increased epithelial damage and inflammation, such as respiratory virus infections, BHR develops and asthma symptoms may appear for the first time., as demonstrated by increased BHR for prolonged periods of time after respiratory virus infections (3)

It is evident that the environmental conditions in which sports and training are practised, is important for the respiratory health of the adolescent athlete. Pollution and harmful chemicals in the environmental air increase the risk for asthma development and BHR in the competing athlete. The effective ventilation of swimming pools is important, and effort should be made to develop not harmful methods of disinfection of the water in swimming pools. Cross-country

skiing competitions should not be carried out in too cold environments, and endurance sports should not be carried out in areas with high air pollution. For the allergic athletes, exposure to aeroallergens may worsen asthma symptoms, and the presence of concomitant allergic rhinitis may reduce quality of life and sports performance (62)

It is thus important that consideration to environmental exposure including climatic conditions is taken when planning sports events, also including when designing arenas for sports events, like swimming pools, ice shrinks and others.

Can preventive and therapeutic measures be taken against asthma development in elite endurance athletes?

If possible endurance and interval training should not be performed in very cold temperatures, nor in outdoor competitions. By inhaling air of -20ºC the EIB of asthmatic children is doubled (63), and the effect upon the athlete with much higher ventilation volumes may be even higher.

As a general advice, competitions in endurance sports should not take place in temperatures lower than -15ºC.

As a primary prevention tool, protection equipment like the heat and water exchangers (64), such as the Lungplus (Hörby, Sweden) (65) and the Jonas Sport mask (Suomen Jonas Oy , Helsiniki, Finland) should be used during training in cold environments. This is as important to use by athletes who may have developed asthma and BHR, as a secondary preventive measure.

Top athletes within sport disciplines prone to develop asthma, should be monitored with regard to the development of symptoms of asthma and BHR. Especially important is the measurement of bronchial responsiveness, the most sensitive methods being either metacholine bronchial provocation or eucapnic voluntary hyperpnoea (66).

Secondary preventive measures will include anti-inflammatory treatment, most important being inhaled steroids. Until now inhaled steroids represent the only treatment, which counteract the respiratory inflammatory processes in the athlete. Inhaled steroids also improve the epithelial healing (35). The current international guidelines for treating EIA should be followed when caring for asthmatic athletes including pre-treatment before exercise with inhaled β_2-agonists and inhaled ipratropium bromide and for symptomatic treatment when having symptoms of asthma. Although the regulations set by WADA and IOC now has been relieved as regards the use of asthma therapy in sports, it has been very well documented the need of objective documentation of bronchial responsiveness as guiding the treatment of asthma in the competing athlete (8). The follow-up and optimal treatment of asthmatic athletes may have life-saving consequences (67). Early diagnosis and early start of treatment may enable the athlete to continue participation in sports and possibly have less symptoms when later on completing the athletic career (68) .

References

1. Larsson K, Ohlsen P, Larsson et al. High prevalence of asthma in cross country skiers. BMJ. 1993;307(6915):1326-9. Epub 1993/11/20.
2. Heir T, Oseid S. Self-reported asthma and exercise-induced asthma symptoms in high-level competetive cross-country skiers. Scand J Med Sci Sports. 1994;4:128-33.
3. Heir T, Aanestad G, Carlsen KH, et al. Respiratory tract infection and bronchial responsiveness in elite athletes and sedentary control subjects. Scand J Med Sci Sports. 1995;5:94-9.
4. 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.
5. Sue-Chu M, Larsson L, Bjermer L. Prevalence of asthma in young cross-country skiers in central Scandinavia: differences between Norway and Sweden. Respir Med. 1996;90(2):99-105.
6. Wilber RL, Rundell KW, Szmedra L,et al. Incidence of exercise-induced bronchospasm in Olympic winter sport athletes. Med Sci Sports Exerc. 2000;32(4):732-7.
7. Rundell KW, Im J, Mayers LB et al. Self-reported symptoms and exercise-induced asthma in the elite athlete. Med Sci Sports Exerc. 2001;33(2):208-13.
8. Fitch KD. An overview of asthma and airway hyper-responsiveness in Olympic athletes. Br J Sports Med. 2012;46(6):413-6. Epub 2012/01/10.
9. Carlsen KH, Anderson SD et al. Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. Allergy. 2008;63(4):387-403. Epub 2008/03/05.
10. Fitch KD. An overview of asthma and airway hyper-responsiveness in Olympic athletes. Br J Sports Med 2012;46(6):413-6..
11. Mannix ET, Farber MO, Palange P et al. Exercise-induced asthma in figure skaters. Chest. 1996;109(2):312-5.
12. Provost Craig MA, Arbour KS, Sestili DC et al.. The incidence of exercise-induced bronchospasm in competitive figure skaters. J Asthma. 1996;33(1):67-71.
13. Leuppi JD, Kuhn M, Comminot C, et al. High prevalence of bronchial hyperresponsiveness and asthma in ice hockey players. Eur Respir J. 1998;12(1):13-6.
14. Lumme A, Haahtela T, Ounap J et al. Airway inflammation, bronchial hyperresponsiveness and asthma in elite ice hockey players. Eur Respir J. 2003;22(1):113-7.
15. Engebretsen L, Steffen K, Alonso JM et al. Sports injuries and illnesses during the Winter Olympic Games 2010. Br J Sports Med. 2010;44(11):772-80. Epub 2010/09/08.
16. Jones RS, Buston MH, Wharton MJ. The effect of exercise on ventilatory function in the child with asthma. Br J Dis Chest. 1962;56:78-86. Epub 1962/04/01.

17. Jones RS, Wharton MJ, Buston MH. The Place of Physical Exercise and Bronchodilator Drugs in the Assessment of the Asthmatic Child. Arch Dis Child. 1963;38:539-45. Epub 1963/12/01.
18. McFadden ER, Jr., Ingram RH, Jr. Exercise-induced asthma: Observations on the initiating stimulus. N Engl J Med. 1979;301(14):763-9. Epub 1979/10/04.
19. McFadden ER, Jr., Lenner KA, Strohl KP. Postexertional airway rewarming and thermally induced asthma. New insights into pathophysiology and possible pathogenesis. J Clin Invest. 1986;78(1):18-25. Epub 1986/07/01.
20. Linn WS, Shamoo DA, Anderson KR et al. Effects of heat and humidity on the responses of exercising asthmatics to sulfur dioxide exposure. Am Rev of Respir Dis 1985;131(2):221-5.
21. Smith CM, Anderson SD, Walsh S et al. An investigation of the effects of heat and water exchange in the recovery period after exercise in children with asthma. Am Rev Respir Dis. 1989;140(3):598-605. Epub 1989/09/01.
22. Anderson SD, Daviskas E. The airway microvasculature and exercise induced asthma. Thorax. 1992;47:748-52.
23. Strauss RH, McFadden ER, Jr., Ingram RH, Jr. et al. Enhancement of exercise-induced asthma by cold air. N Engl J Med. 1977;297(14):743-7. Epub 1977/10/06.
24. Deal EC, Jr., McFadden ER, Jr., Ingram RH, Jr. et al.. Hyperpnea and heat flux: initial reaction sequence in exercise-induced asthma. J Appl Physiol. 1979;46(3):476-83.
25. Jaeger JJ, Deal EC, Jr., Roberts DE, Ingram RH, Jr., McFadden ER, Jr. Cold air inhalation and esophageal temperature in exercising humans. Med Sci Sports Exerc. 1980;12(5):365-9.
26. Deal EC, Jr., McFadden ER, Jr., Ingram RH, Jr. et al. Role of respiratory heat exchange in production of exercise-induced asthma. J Appl Physiol. 1979;46(3):467-75.
27. McFadden ER, Jr., Nelson JA, Skowronski ME et al.. Thermally induced asthma and airway drying. AmJRespirCrit Care Med. 1999;160(1):221-6.
28. Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is... J Allergy Clin Immunol. 2000;106(3):453-9.
29. Eveloff JL, Warnock DG. Activation of ion transport systems during cell volume regulation. Am J Physiol. 1987;252(1 Pt 2):F1-10. Epub 1987/01/01.
30. Hallstrand TS, Henderson WR, Jr. Role of leukotrienes in exercise-induced bronchoconstriction. Curr Allergy Asthma Rep. 2009;9(1):18-25. Epub 2008/12/10.
31. Carlsen KH, Oseid S, Odden H et al. The response to heavy swimming exercise in children with and without bronchial asthma. In: Morehouse CA, editor. Children and Exercise XIII. Champaign, Illinois: Human Kinetics Publishers, Inc.; 1989. p. 351-60.
32. Sue-Chu 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(2):597-601.
33. Chimenti L, Morici G, Paterno A, Bonanno A, Siena L, Licciardi A, et al. Endurance training damages small airway epithelium in mice. AmJRespirCrit Care Med. 2007;175(5):442-9.

34. Davis MS, McKiernan B, McCullough S et al. Racing Alaskan sled dogs as a model of "ski asthma". Am J Respir Crit Care Med. 2002;166(6):878-82. Epub 2002/09/17.
35. Freishtat RJ, Watson AM, Benton AS et al. Asthmatic airway epithelium is intrinsically inflammatory and mitotically dyssynchronous. Am J Respir Cell Mol Biol. 2011;44(6):863-9. Epub 2010/08/14.
36. Bougault V, Turmel J, St-Laurent J.. Asthma, airway inflammation, and epithelial damage in swimmers and cold-air athletes. Eur Respir J. 2009;33(4):740-6.
37. Bougault V, Turmel J, Boulet LP. Bronchial challenges and respiratory symptoms in elite swimmers and winter sport athletes: Airway hyperresponsiveness in asthma: its measurement and clinical significance. Chest. 2010;138(2 Suppl):31S-7S. Epub 2010/04/07.
38. Chimenti L, Morici G, Paterno A et al. Bronchial epithelial damage after a half-marathon in nonasthmatic amateur runners. Am J Physiol Lung Cell Mol Physiol. 2010;298(6):L857-62. Epub 2010/04/07.
39. Bolger C, Tufvesson E, Anderson SD et al. The effect of inspired air conditions on exercise-induced bronchoconstriction and urinary CC16 levels in athletes. J Appl Physiol. 2011. Epub 2011/07/30.
40. Bolger C, Tufvesson E, Sue-Chu M et al. Hyperpnea-induced bronchoconstriction and urinary CC16 levels in athletes. Med Sci Sports Exerc. 2011;43(7):1207-13. Epub 2010/12/07.
41. Romberg K, Bjermer L, Tufvesson E. Exercise but not mannitol provocation increases urinary Clara cell protein (CC16) in elite swimmers. Respir Med. 2011;105(1):31-6. Epub 2010/08/11.
42. Hallstrand TS, Moody MW, Aitken ML et al. Airway immunopathology of asthma with exercise-induced bronchoconstriction. J Allergy Clin Immunol. 2005;116(3):586-93.
43. Hallstrand TS, Moody MW, Wurfel MM et al. Inflammatory basis of exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 2005;172(6):679-86.
44. Besnard AG, Togbe D, Couillin I et al. Inflammasome-IL-1-Th17 response in allergic lung inflammation. J mol cell biol. 2012;4(1):3-10. Epub 2011/12/08.
45. Park C, Stafford C, Lockette W. Exercise-induced asthma may be associated with diminished sweat secretion rates in humans. Chest. 2008;134(3):552-8. Epub 2008/07/22.
46. Nejsum LN, Kwon TH, Jensen UB et al. Functional requirement of aquaporin-5 in plasma membranes of sweat glands. Proc Natl Acad Sci U S A. 2002;99(1):511-6. Epub 2002/01/05.
47. Filipe JA, Falcao-Reis F, Castro-Correia J et al. Assessment of autonomic function in high level athletes by pupillometry. Auton Neurosci. 2003;104(1):66-72. Epub 2003/02/01.
48. Knopfli BH, Bar-Or O. Vagal activity and airway response to ipratropium bromide before and after exercise in ambient and cold conditions in healthy cross-country runners. Clin J Sport Med. 1999;9(3):170-6. Epub 1999/10/08.
49. Knopfli BH, Bar-Or O, Araujo CG. Effect of ipratropium bromide on EIB in children depends on vagal activity. Med Sci Sports Exerc. 2005;37(3):354-9. Epub 2005/03/03.

50. Deal EC, Jr., McFadden ER, Jr., Ingram RH, Jr. et al. Effects of atropine on potentiation of exercise-induced bronchospasm by cold air. J Appl Physiol. 1978;45(2):238-43.
51. Stadelmann K, Stensrud T, Carlsen KH. Respiratory symptoms and bronchial responsiveness in competitive swimmers. Med sci sports exerc. 2011;43(3):375-81. Epub 2010/08/07.
52. Stensrud T, Mykland KV, Gabrielsen K et al. Bronchial hyperresponsiveness in skiers: field test versus methacholine provocation? Med Sci Sports Exerc. 2007;39(10):1681-6. Epub 2007/10/03.
53. Bernard A, Carbonnelle S, de Burbure C, et al. Chlorinated pool attendance, atopy, and the risk of asthma during childhood. Enviro Health Perspect. 2006;114(10):1567-73.
54. Font-Ribera L, Villanueva CM, Nieuwenhuijsen MJ et al. Swimming Pool Attendance, Asthma, Allergies and Lung Function in the ALSPAC Child Cohort. Am J Respir Crit Care Med. 2011;183(5):582-8..
55. Moreira A, Delgado L, Palmares C et al. Competitive swimmers with allergic asthma show a mixed type of airway inflammation. Eur Respir J. 2008;31(5):1139-41. Epub 2008/05/02.
56. Helenius IJ, Rytila P, Metso T et al. Respiratory symptoms, bronchial responsiveness, and cellular characteristics of induced sputum in elite swimmers. Allergy. 1998;53(4):346-52.
57. Bougault V, Loubaki L, Joubert P et al. Airway remodeling and inflammation in competitive swimmers training in indoor chlorinated swimming pools. J Allergy Clin Immunol. 2012;129(2):351-8, 8 e1. Epub 2011/12/27.
58. Piacentini GL, Rigotti E, Bodini A et al. Airway inflammation in elite swimmers. J Allergy Clin Immunol. 2007;119(6):1559-60; author reply 60-1. Epub 2007/04/03.
59. Weisel CP, Richardson SD, Nemery B et al. Childhood asthma and environmental exposures at swimming pools: state of the science and research recommendations. Environmen Health Perspect. 2009;117(4):500-7. Epub 2009/05/15.
60. Rundell KW. High levels of airborne ultrafine and fine particulate matter in indoor ice arenas. Inhal Toxicol. 2003;15(3):237-50.
61. McConnell R, Berhane K, Gilliland F et al. Asthma in exercising children exposed to ozone: a cohort study. Lancet. 2002;359:386-91.
62. Bonini S, Bonini M, Bousquet J et al. Rhinitis and asthma in athletes: an ARIA document in collaboration with GA2LEN. Allergy. 2006;61(6):681-92. Epub 2006/05/09.
63. Carlsen KH, Engh G, Mork M et al 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(2):308-15. Epub 1998/06/09.
64. Kippelen P, Fitch KD, Anderson SD et al. Respiratory health of elite athletes - preventing airway injury: a critical review. Br J Sports Med. 2012;46(7):471-6. Epub 2012/04/24.
65. Millqvist E, Bake B, Bengtsson U et al Prevention of asthma induced by cold air by cellulose-fabric face mask. Allergy. 1995;50(3):221-4.

66. Stadelmann K, Stensrud T, Carlsen KH. Respiratory symptoms and bronchial responsiveness in competitive swimmers. Med Sci Sports Exerc. 2011;43(3):375-81. Epub 2010/08/07.
67. Becker JM, Rogers J, Rossini G, Mirchandani H, D'Alonzo GE, Jr. Asthma deaths during sports: report of a 7-year experience. J Allergy Clin Immunol. 2004;113(2):264-7.
68. Helenius I, Rytila P, Sarna S, Lumme A, Helenius M, Remes V, et al. Effect of continuing or finishing high-level sports on airway inflammation, bronchial hyperresponsiveness, and asthma: a 5-year prospective follow-up study of 42 highly trained swimmers. JAllergy ClinImmunol. 2002;109(6):962-8.

Figure 1. Water content of air at different temperatures at 50% and 100% relative humidity. Source Wikipedia: Relative humidity. 03.04.2012.

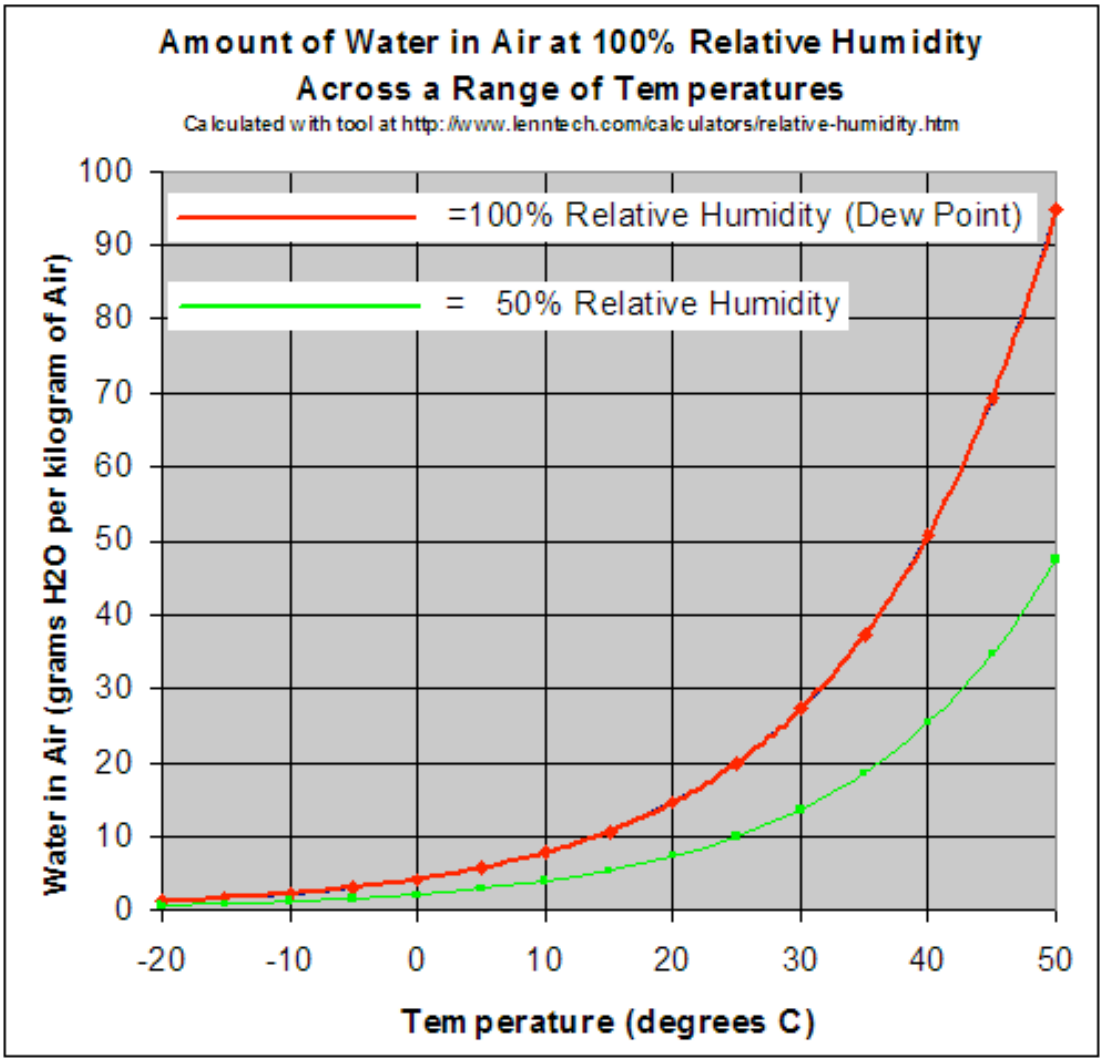

Figure 2. Hypothesis of pathogenic mechanisms for the development of asthma in elite athletes within cold air sports.

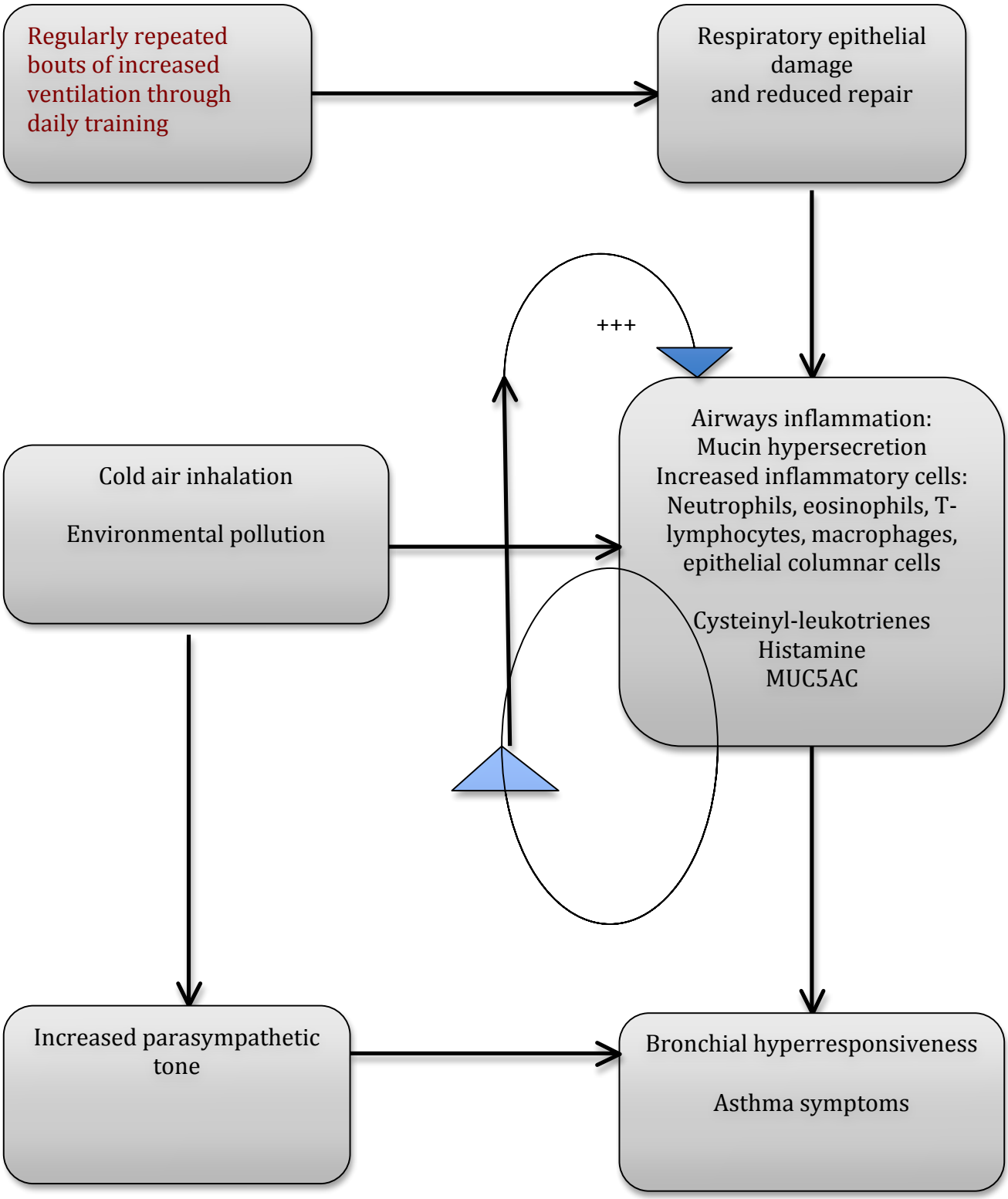

Figure texts:

Figure 1. Water content of air at different temperatures at 50% and 100% relative humidity. Source Wikipedia: Relative humidity. 03.04.2012.

Figure 2. Hypothesis of pathogenic mechanisms for the development of asthma in elite athletes within cold air sports.

What are the new findings:

This article presents the effect of repeated exposures to cold air inhalation to the respiratory tract in competing athletes, and exercising children and adolescents. A novel hypothesis is presented to explain the marked increased prevalence of exercise induced asthma and bronchial hyperresponsiveness in elite athletes competing in outdoor endurance sports during winter time in cold climates. Regularly repeated prolonged bouts of marked increased ventilation during training and competitions with exposure to cold air cause respiratory epithelial damage, airways inflammation and resulting bronchial hyperresponsivness. Furthermore, both endurance training and cold air exposure causes increased parasympathetic tone, which further enhances the bronchial hyperresponsiveness. These stimuli causes the asthmatic symptoms occurring so frequent in cross-country skiers, skiers of Nordic combined, biathlon and other outdoor winter sports.

How might it impact on clinical practice in the near future?

This underlines the need for early diagnosis, regular medical follow-up with regular use of anti-inflammatory treatment foremost bys use of inhaled corticosteroids when bronchial hyperresponsiveness is diagnosed. Furthermore, the endurance athlete with asthma and bronchial hyperrepsonsiveness will probably benefit from inhaled treatment blocking increased parasymptatheitic tone like inhaled ipratropium bromide and inhaled tiotropium.