

Air Quality and Exercise-Induced Bronchoconstriction in Elite Athletes

Kenneth W. Rundell, PhD^{a,b,*}, Malcolm Sue-Chu, MB ChB, PhD^{c,d}

KEYWORDS

• Air pollution • Cold air • Dry air • Exercise • Breathing • Asthma • Airway damage • Athlete

KEY POINTS

- The requisite warming and humidification of the inspired air at high ventilation rates can result in airway drying and subsequent damage, inflammation, and bronchial hyperresponsiveness.
- Data from bronchial challenge test studies on the ice-rink athlete show consistently high rates of exercise-induced bronchoconstriction, and recent evidence implicates inhalation of airborne fine and ultrafine particles emitted in the exhaust of fossil-fueled ice-resurfacing machines.
- Replacement of fossil-fueled resurfacing equipment with electric ice-resurfacing equipment in indoor ice arenas would decrease the level of harmful pollutants.

INTRODUCTION

Aerobic exercise results in cardiovascular changes that support improved health and longevity. However, exercise in cold/dry air or in polluted environments can cause airway injury and airway hyperresponsiveness (AHR), and may lead to the development of asthma. Winter sports athletes compete in both outdoor and indoor environments in conditions that may be harmful to the airways. However, for these athletes, training is a year-round activity and depending on the training venue, exposure may be continuous. The outdoor winter athlete is exposed to the cold/dry air

Funding Sources: No current funding.

Conflict of Interest: Previous Consultant for Merck, Inc. Current Consultant for Pharmaxis Inc (K.W. Rundell). None (M. Sue-Chu).

^a Pharmaxis Inc, Philadelphia, PA 19341, USA; ^b Commonwealth Medical College, Scranton, PA 18509, USA; ^c Department of Thoracic Medicine, St Olavs Hospital, Trondheim University Hospital, Postbox 3250 Sluppen, NO-7006 Trondheim, Norway; ^d Department of Circulation and Medical Imaging, Institute of Circulation and Imaging, Norwegian University of Science and Technology, Trondheim, Norway

* Corresponding author. Medical Affairs, One East Uwchlan Avenue, Suite 405, Exton, PA 19341.

E-mail address: Ken.rundell@pharmaxis.com

Immunol Allergy Clin N Am 33 (2013) 409–421

<http://dx.doi.org/10.1016/j.iac.2013.02.009>

immunology.theclinics.com

0889-8561/13/\$ – see front matter © 2013 Elsevier Inc. All rights reserved.

during the competitive season and may also be exposed to traffic-related pollutants and ozone during off-season training, depending on the athlete's training location. The ice-rink athlete could be exposed to high pollutants emitted from ice-resurfacing machines as well as to cold/dry air throughout the competitive and noncompetitive seasons.

Exercise-induced bronchoconstriction (EIB) is the transient narrowing of the airways usually occurring within 20 minutes after exercise, but can occur during the exercise, and spontaneously resolves within 30 to 60 minutes. Theories for pathogenesis of EIB include the hyperosmolar hypothesis, which postulates hyperpnea-induced drying of the airways with subsequent increase in cell osmolality and release of bronchoconstricting mediators from inflammatory cells.¹ The airway-cooling hypothesis is based on a reduction of intra-airway temperature during exercise and development of a reactive hyperemia after exercise in response to airway cooling.² Smooth-muscle contraction in response to inflammatory mediators and a reduction in airway caliber from hyperemia have been suggested to be responsible for EIB.³ However, EIB is not a universal response to exercise in all athletes, and other factors such as environmental and personal risk factors are involved in determining the response.⁴ Environmental factors, such as quality, relative humidity, and temperature of the inspired air during training and competition, affect all athletes, while allergens are of importance in atopic athletes. On an individual level, factors such as the response of the parasympathetic nervous system, the degree of neurogenic-mediated immune inflammation, and genetic susceptibility may be significant. However, the interaction between environmental and personal risk factors may determine the response of the airway to strenuous exercise.⁴

EFFECT OF COLD AIR

Cold air can serve as a more severe stimulus to the airway, primarily because the air is dry, even when fully saturated with water vapor. The relationship between the water-vapor content in air at a given relative humidity and temperature is curvilinear (**Fig. 1**).⁵ At an ambient temperature of -10° , 0° , $+10^{\circ}$, and 37°C the maximum water content is 3, 5, 9, and 44 mg/L, respectively. Thus, conditioning of air from -10°C to body temperature requires the addition of 41 mg of water per liter of air, and causes a decrease in intra-airway temperature. At a ventilation rate of 60 L/min for 4 minutes, the decrease in temperature is 4°C greater when breathing air at -17°C , in comparison with air at room temperature.⁶ Expiratory water losses and, thus, dehydration of the airways will be greater during training/competition at lower ambient temperatures. The long-term effects of exercise in cold/dry air have not been investigated in longitudinal studies in human winter-sports athletes. Most studies evaluating the prevalence of EIB in both winter and summer athletes are cross-sectional in design and report on a specific sport population with a typically small number of subjects. However, a decrease of lung function has been observed in 3 cross-country skiers followed over a period of 9 to 12 years.⁷ In addition, the prevalence of respiratory symptoms and AHR to direct stimuli is increased together with evidence of airway inflammation and remodeling in cross-sectional studies.⁷⁻⁹ Neutrophilic inflammation in the submucosa with lymphocyte aggregates is seen in bronchial biopsies in cross-country skiers,^{8,9} whereas increased counts of neutrophils and, to a lesser degree, of eosinophils are present in induced sputum in ice hockey players.¹⁰

EFFECT OF AIRBORNE POLLUTION

Exercise in environments containing high levels of respirable pollutants has both acute and chronic effects on the airways and the cardiovascular system; this is of special

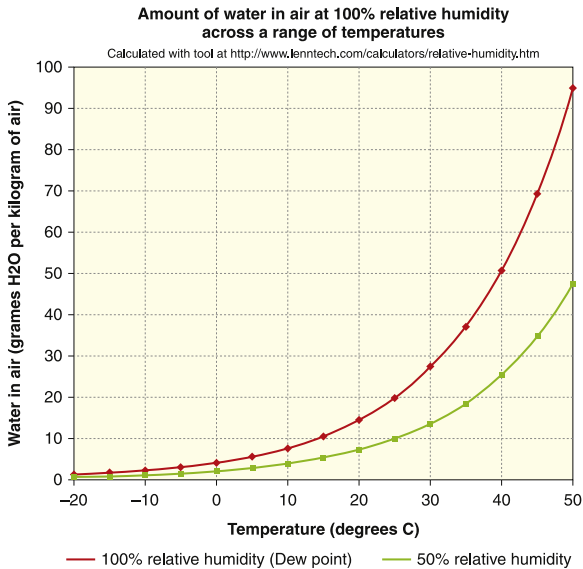


Fig. 1. Curvilinear relationship between water content in air and ambient temperature.

interest to elite athletes because of the high ventilations they achieve and sustain during exercise.^{11–13} The serious athlete may be at greater risk to these environmental influences than the recreational athlete because of the greater overall exposure and increased deposition of pollutants from the high training volumes at increased minute ventilation. Ultrafine particles (UPM, particles <100 nm diameter; Fig. 2), those that are emitted in high concentrations from internal combustion engines, have greater deposition efficiency than larger particles,^{11,12} are highly oxidative,¹⁴ and induce pulmonary inflammation (Fig. 3).^{15–19}

A causative relationship between exposure to air pollution and the development of asthma, AHR, and increased asthma exacerbations is supported by several

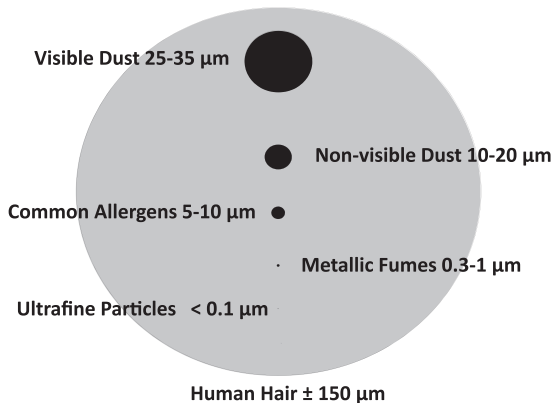


Fig. 2. Size relationship between ultrafine particles, metallic fumes, common allergens, non-visible dust, and visible dust within a cross section of a human hair.

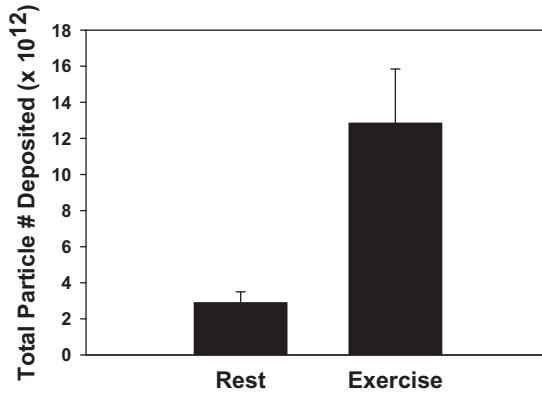


Fig. 3. Total number of deposited particles during rest and 1 hour of moderate exercise at 38 ± 9.5 L/min ventilation. Deposition of particles of 26 ± 1.6 nm diameter during exercise was found to be more than 4.5-fold higher than at rest because of the increase in deposition fraction of the smaller particles coupled with increased minute ventilation. (*Redrawn from Daigle CC, Chalupa DC, Gibb FR, et al. Ultrafine particle deposition in humans during rest and exercise. Inhal Toxicol 2003;15(6):539–52.*)

studies.^{20–26} Urban and occupational air quality has recently received much attention, although few studies specifically address the consequence of exercise in high-particulate ambient air environments. Several emission-related airborne pollutants have been identified as harmful: ozone (O_3), sulfur dioxide (SO_2), nitrogen oxides (NO_x) and particulate matter ($PM_{2.5}$, particles <2.5 μm diameter). Ozone, nitrogen dioxide, and freshly generated particulate matter (PM) from internal combustion engines are the primary pollutants of concern in the outdoor environment, although indoor air quality (AQ) is of importance; trichloramine (NCl_3), a gas formed in chlorinated pools, has been implicated in swimmer asthma.²⁷

Investigators have examined the relationship between ice-rink AQ²⁸ and EIB, and have associated the high prevalence of EIB identified in skating athletes to inhalation of PM_1 (PM <1 μm diameter).^{21–23} The 20% to 50% prevalence of EIB reported in skaters^{21,22,29,30} is much higher than the estimated 8% to 10% prevalence of asthma in the United States. Chronic ventilation of cold/dry air during sport training and competition, combined with high levels of PM_1 , may enhance the expression of, or directly cause, EIB and airway damage. Likewise, urban athletic fields and school playgrounds may present a major health concern affecting all ages and genders. Multiple (62 days) measurements of air pollutants at a university soccer field in close proximity to a major highway have shown PM_1 at extremely high levels (**Fig. 4**),²⁴ and significant decreases in lung function in the college soccer players using these fields has recently been reported.³¹

MECHANISMS

Cold/Dry Air-Induced Airway Injury

Epithelial injury and mucosal inflammation in the airways caused by hyperpnea has been demonstrated directly in animal studies and indirectly in human studies; the presence of inflammatory cells can lead to AHR. In dogs, acute hyperpnea of the peripheral airways with dry air damages the mucosa and induces inflammatory changes and microvascular leakage that persists for more than 24 hours.^{32,33} When hyperpnea is repeated over a 4-day period, mucosal edema develops, and is followed by repair of

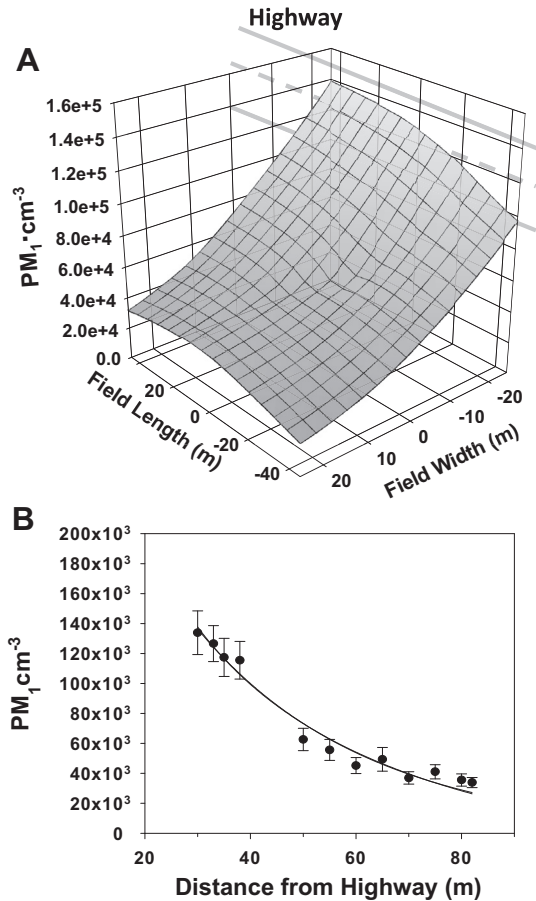


Fig. 4. (A) A 3-dimensional blanket graph of the mean values for 62 days at 12 locations at a soccer field located next to a high-traffic roadway shows the increased count at the locations nearest the roadway, with the lower counts furthest away from the roadway. (B) The decline in number count moving away from the roadway follows a curvilinear order ($r = -0.99$) and is due to dispersion and particle agglomeration. (Redrawn from Rundell KW, Caviston R, Hollenbach AM, et al. Vehicular air pollution, playgrounds, and youth athletic fields. *Inhal Toxicol* 2006;18(8):541–7.)

the epithelial damage and restoration of normal morphology within 1 week.³⁴ Similar changes are seen in the bronchiolar epithelial turnover without inflammation in mice, after endurance training at low to moderate intensity at room temperature over 45 days.³⁵ At 24 to 48 hours after completion of an 1100-mile endurance race in subfreezing conditions there is, in addition to mucosal edema, accumulation of intraluminal debris and an increase of inflammatory cells in the bronchoalveolar lavage (BAL) fluid in racing sled dogs.³⁶ Furthermore, when horses were exercised at 4°C in comparison with exercise at 25°C,³⁷ an increased number of ciliated epithelial cells was present in BAL fluid and a local preferential upregulation of the T-helper type 2 cytokines interleukin (IL)-4, IL-5, and IL-10, as well as cytokines IL-2 and IL-6, was noted.³⁸

Clara cell protein 16 (CC16) is a protein secreted by Clara cells localized predominantly in the bronchioli, and has an anti-inflammatory function. Increased levels of this

protein in the blood and urine may indicate epithelial damage.³⁹ Recent studies have shown an increase in urinary excretion of this protein after 8 minutes of hyperpnea of dry air,⁴⁰ and also after a similar duration of exercise at near maximal aerobic capacity breathing cold dry (4°C, 37% relative humidity) and warm humid (25°C, 94% relative humidity) air. Of note, the increase in urinary excretion of CC16 was blunted by the inhalation of warm humid air.⁴¹

Pollution-Induced Airway Injury

Many toxicologic pathways have been proposed in establishing the mechanism for pollution-related airway damage. Evidence for airway inflammation^{26,42–45} and oxidative stress^{46–49} have been identified after both PM exposure and ozone exposure. Likewise, several studies have shown that high particulate loads increase bronchiolar fibrosis.^{50–52}

McCreanor and colleagues²⁶ identified markers of inflammation and reductions in forced expiratory volume in the first 1 second of exhalation (FEV₁) and forced vital capacity (FVC) in 60 mild and moderate asthmatic patients after walking for 2 hours along a London street or in a park. Reductions of up to 6.1% in FEV₁ and 5.4% in FVC after walking on the street were significantly larger than after walking in the park ($P = .04$ and $P = .01$), with $P < .005$ at some time points (Fig. 5). The effects were greater for the moderate asthmatics than for the mild asthmatics, and these changes were accompanied by increases in sputum myeloperoxidase (MPO), a marker of neutrophilic inflammation: 24.5 ng/mL and 4.24 ng/mL for street and park walking, respectively. These changes were associated with exposure to ultrafine particles and elemental carbon. Likewise, Salvi and colleagues⁵³ showed increased neutrophils, mast cells, CD4⁺ and CD8⁺ T lymphocytes, and upregulation of the endothelial adhesion molecules intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 in bronchial tissue after exposure to diesel exhaust. Increased sputum neutrophils and MPO were noted after 4 hours of controlled exposure to diesel exhaust without changes in inflammatory markers in peripheral blood.⁵⁴ These studies support increased neutrophilic inflammatory pathway from pollution exposure that is localized to the airways.

Reactive oxidants, produced in response to the inhalation of air pollutants, can stress the airway antioxidant system and subsequently harm cellular components, control the expression of genes, and lead to airway inflammation and airway hyperreactivity. In a cohort of 1610 schoolchildren, Islam and colleagues⁴⁹ evaluated the effects of genetic variants of glutathione S-transferase (GST) and exercise in high ozone. GST is expressed in the lungs and is essential for glutathione homeostasis, which provides protection from by-products of oxidative stress. An increased risk of asthma development was identified from ozone exposure in individuals with the functional sequence variant in GSTP1 single-nucleotide polymorphism (SNP) at codon 105 (Ile105 homozygotes).⁴⁹ This study suggests a strong relationship between airway oxidative stress and the development and severity of asthma. Ercan and colleagues⁵⁵ genotyped a total of 196 children with mild asthma, 116 children with moderate to severe asthma, and 255 controls for GST variants. Systemic malondialdehyde (MDA, a marker of lipid peroxidation) increased, and reduced glutathione (GSH) decreased, in mild to severe asthmatics compared with healthy controls ($P < .001$). Further, regression analysis identified asthma and asthma severity associated with oxidative stress. The GSTP1 Ile105 homozygote was more frequent among asthmatics, whereas the GSTP1 Val105 homozygote was less frequent and was associated with asthma severity.⁵⁵ The GSTP1 Ile105 homozygote has been associated with an increased risk of asthma in children who participated in outdoor sports in

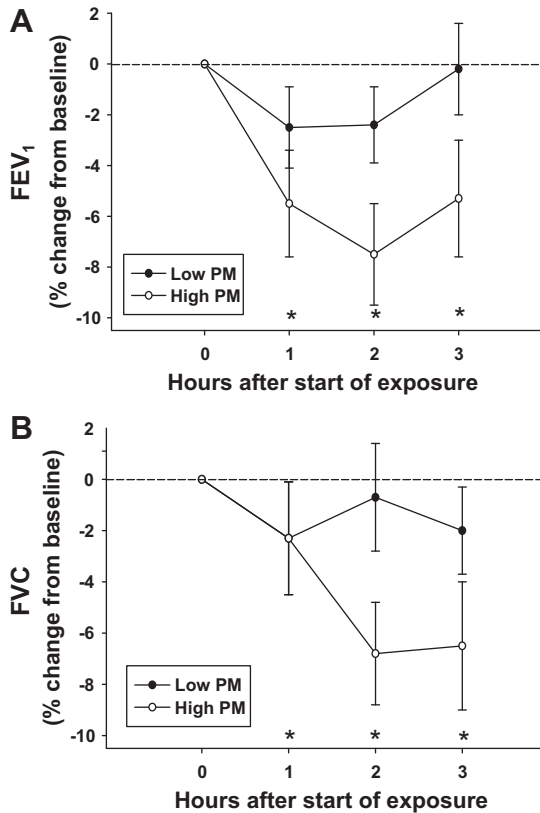


Fig. 5. Sixty adults with mild or moderate asthma were exposed to low ambient particulate matter (PM) and high ambient PM on randomized separate days by walking for 2 hours in each condition. Lung function was measured at 1, 2, 3, 5, 7, and 22 hours from the beginning of the walk. Percent change in forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) from baseline values for the first 3 hours are depicted in (A) and (B), respectively. Change in FEV₁ was significantly lower for the first 7 hours ($P < .05$), and FVC was significantly lower for the first 3 hours from baseline. (Redrawn from McCreanor J, Cullinan P, Nieuwenhuijsen MJ, et al. Respiratory effects of exposure to diesel traffic in persons with asthma. *N Engl J Med* 2007;357(23):2348–58.)

high-ozone communities (Fig. 6).⁴⁹ Zaman and colleagues⁵⁶ found that S-nitrosoglutathione (GSNO) is formed by the reactions of GSH with nitric oxide in the presence of oxygen, and acts as a potent bronchodilator and aids in cilia motion. Low levels of GSNO, found in asthmatics and patients with cystic fibrosis with chronically low GSH, could be the result of air-pollution-related GSH depletion. It has been shown that low levels of GSNO (0.5–1 μ M) increase 5-lipoxygenase (5-LO, an important enzyme in the cysteinyl leukotriene pathway) activity to 6-fold, whereas GSNO levels greater than 5 μ M inhibit 5-LO activity and leukotriene (LT) generation.⁵⁶ This observation provides an explanation for the predominately LT-driven AHR reported in ice hockey players who are exposed to ice-resurfacing machine exhaust fumes²³ as well as the high urinary levels of LT E₄ in asthmatics exposed to fine PM.⁵⁷ These findings highlight the importance of the airway antioxidant system as well as the genetic influence of environmental exposure and risk in the development of asthma.

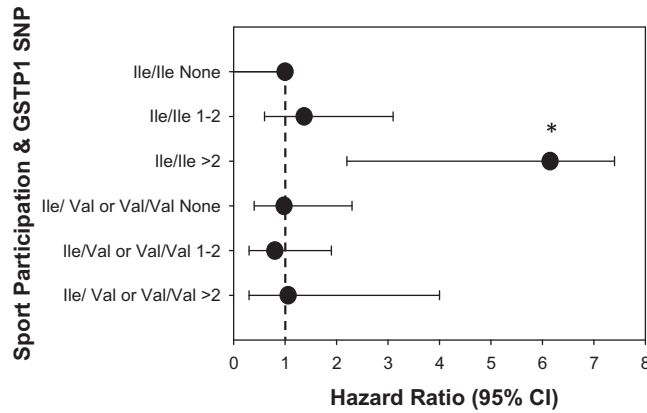


Fig. 6. Using a 2-single nucleotide polymorphism (SNP) model, the Glutathione-S-transferase (GST) P1 Ile105 homozygotes who participated in 3 sports in high ozone communities showed the highest risk of developing asthma (hazard ratio 6.15; 95% confidence interval [CI] 2.2–7.4). (Data from Islam T, Berhane K, McConnell R, et al. Glutathione-S-transferase (GST) P1, GSTM1, exercise, ozone and asthma incidence in school children. *Thorax* 2008;64(3):197–202.)

Recently, Hyseni and colleagues⁵⁸ suggested that elevated arginase II activity and its expression in human bronchial epithelial cells is induced by PM exposure, and may play a role in the response by asthmatics by decreasing L-arginine concentrations, leading to a shift toward the production of harmful mediators such as superoxide ions and peroxynitrite. These mediators likely play a major role in the pathogenesis of asthma.⁵⁹ In an 8-year prospective study of 1759 children, Gauderman and colleagues²⁰ found that clinically statistically significant deficits in the growth of FEV₁ were associated with nitrogen dioxide ($P = .005$), acid vapor ($P = .004$), PM_{2.5} ($P = .04$), and elemental carbon ($P = .007$). PM exposure can directly induce expression of genes involved in airway-wall fibrosis through nuclear factor κ B-mediated and transforming growth factor β -mediated mechanisms, and may play a major role in the airway obstruction observed in individuals chronically exposed to high PM.⁶⁰

PREVALENCE OF AIRWAY DYSFUNCTION IN WINTER ATHLETES

The precise cause of the high prevalence of EIB^{22,29,30,61} in winter athletes is unique to the respective training and competition environments. The outdoor winter athlete is exposed to cold/dry air at repeated high minute ventilations during winter sports competition and training. The prevalence of EIB in Nordic skiers has been reported to be 25% to 50%.^{62–64} One study found as many as 78% of elite cross-country skiers having symptoms and/or hyperresponsive airways.⁶⁵ A more recent study of 46 elite Swedish Nordic skiers reported a lower prevalence of 17% for AHR.⁶⁶

The prevalence of EIB in cold-weather athletes is much higher than the 4% to 15% estimated for the nonathlete population or for the warm-weather athlete.^{61,67,68} For the 1998 US Winter Olympic Team, 50% of the Nordic skiers, 43% of the speed skaters, 21% of the figure skaters, 17% of the Nordic combined team, 15% of the ice hockey players, and 9% of the long-track speed skaters had confirmed EIB and/or asthma.⁶¹ The confined space of indoor ice arenas and multiple ice-resurfacing by gas- or propane-powered machines presents significant health risks to the skating athlete. The high prevalence of EIB in skaters^{10,21,22,29,30,61,69} and the documented high levels

of PM²⁸ provide evidence for a causal relationship for EIB and decline in resting lung function. High ventilation rates achieved during training and competition will enhance PM deposition efficiency in the lung, making this athlete population especially susceptible to effects of PM exposure. These indoor competitors experience a greater prevalence of EIB, more asthma-like symptoms, and a greater degree of small-airway dysfunction than do outdoor winter athletes.^{10,21,22,69} A large percentage of ice-arena athletes who have low resting pulmonary function consistent with chronic small-airway inflammation have been identified.^{21,22} Rundell and colleagues²² found that 39.5% of elite women hockey players presented symptoms of asthma and 21% demonstrated EIB, while Lumme and colleagues¹⁰ found that 52% of elite Finnish hockey players reported symptoms and 24% had bronchial hyperresponsiveness (BHR) to a histamine challenge. Considering that ice-arena athletes train under conditions whereby ambient temperature and humidity are not as extreme as for their outdoor counterparts, this finding seems paradoxical to the hypothesis that EIB in winter athletes is caused by thermal damage to the airways.⁷⁰

In swimmers, chloramines above the water may trigger EIB and likely generate oxidative stress in the airways. Swimmers with longer duration of exposure tend to have a higher prevalence of EIB.^{27,71,72} In a 5-year prospective follow-up study, a decreased incidence of EIB and airway inflammation was observed after discontinuation of swimming by elite swimmers.⁷³ Castricum and colleagues⁷⁴ evaluated 33 elite swimmers undergoing eucapnic voluntary hyperpnea (EVH), an 8-minute swim challenge, and an 8-minute laboratory cycle challenge in ambient air. Thirty-nine percent had a clinical diagnosis of asthma and 55%, 3%, and 12% tested positive by EVH, swim test, and cycle test, respectively.

SUMMARY

A true prevalence of EIB in elite winter athletes is difficult to obtain because of inconsistencies in the way a diagnosis is made. Some studies have used direct challenge tests, others have used a variety of indirect bronchial challenge tests, and others have relied on questionnaires or self-reported symptoms. The outdoor winter athlete typically trains and competes in a cold environment where air water content is quite low. The requisite warming and humidification of the inspired air at high ventilation rates can result in airway drying and subsequent damage, inflammation, and BHR. Data from bronchial challenge test studies on the ice-rink athlete show consistently high rates of EIB, and recent evidence implicates inhalation of airborne fine and ultra-fine particles emitted in the exhaust of fossil-fueled ice-resurfacing machines. Not only are these athletes at risk, but those who train in the urban environment where pollution is high are also at potential risk for airway damage. Likewise, inhalation of airborne Teflon particles from fluorinated waxes in the confines of the waxing room may be an added risk to the skier. Several studies have shown evidence of high oxidative stress, airway inflammation, and airway remodeling related to particle inhalation. Although swimmers are not winter athletes per se, the serious swimmer is exposed to high concentrations of trichloramines at the pool-surface level all the year round. Trichloramine is highly oxidative and has been linked to asthma and EIB in swimmers, and this is discussed in the article by Bougault and Boulet elsewhere in this issue. The harsh conditions endured by the outdoor winter athlete cannot be changed. However, the use of a heat-exchanger mask has been shown to be as effective as pretreatment with albuterol⁷⁵ in blocking the EIB response, and could be used in training when conditions are extremely cold. It has also been suggested that training through mild respiratory infections places the airways at additional risk for damage, and should

not be done. Replacement of fossil-fueled resurfacing equipment with electric ice-resurfacing equipment in indoor ice arenas would decrease the level of harmful pollutants. For the athlete who trains in the urban environment, it would be wise to design training routes around low-traffic hours and in low-traffic areas. Of course the athlete will not be able to avoid all hazardous conditions, but an attempt to minimize exposure could have a beneficial and significant effect.

REFERENCES

1. Anderson SD. Is there a unifying hypothesis for exercise-induced asthma? *J Allergy Clin Immunol* 1984;73:660–5.
2. McFadden ER. Hypothesis: exercise-induced asthma as a vascular phenomenon. *Lancet* 1990;1:880–3.
3. Anderson SD, Kippelen P. Exercise-induced bronchoconstriction: pathogenesis. *Curr Allergy Asthma Rep* 2005;5:116–22.
4. Moreira A, Delgado L, Carlsen KH. Exercise-induced asthma: why is it so frequent in Olympic athletes? *Expert Rev Respir Med* 2011;5:1–3.
5. Available at: http://en.wikipedia.org/wiki/Relative_humidity. Accessed December 12, 2012.
6. McFadden ER Jr, Denison DM, Waller JF, et al. Direct recordings of the temperatures in the tracheobronchial tree in normal man. *J Clin Invest* 1982;69:700–5.
7. Vergès S, Flore P, Blanchi MP, et al. A 10-year follow-up study of pulmonary function in symptomatic elite cross-country skiers—athletes and bronchial dysfunctions. *Scand J Med Sci Sports* 2004;14:381–7.
8. Karjalainen EM, Laitinen A, Sue-Chu M, et al. Evidence of airway inflammation and remodeling in ski athletes with and without bronchial hyperresponsiveness to methacholine. *Am J Respir Crit Care Med* 2000;161:2086–91.
9. 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;158:597–601.
10. Lumme A, Haahtela T, Ounap J, et al. Airway inflammation, bronchial hyperresponsiveness and asthma in elite ice hockey players. *Eur Respir J* 2003;22:113–7.
11. Daigle CC, Chalupa DC, Gibb FR, et al. Ultrafine particle deposition in humans during rest and exercise. *Inhal Toxicol* 2003;15(6):539–52.
12. Chalupa DC, Morrow PE, Oberdörster G, et al. Ultrafine particle deposition in subjects with asthma. *Environ Health Perspect* 2004;112(8):879–82.
13. Oravijärvi K, Pietikäinen M, Ruuskanen J, et al. Effects of physical activity on the deposition of traffic-related particles into the human lungs in silico. *Sci Total Environ* 2011;409(21):4511–8.
14. Li N, Hao M, Phalen RF, et al. Particulate air pollutants and asthma. A paradigm for the role of oxidative stress in PM-induced adverse health effects. *Clin Immunol* 2003;109(3):250–65.
15. Campen MJ, Lund A, Rosenfeld M. Mechanisms linking traffic-related air pollution and atherosclerosis. *Curr Opin Pulm Med* 2012;18(2):155–60.
16. Frampton MW, Utell MJ, Zareba W, et al. Effects of exposure to ultrafine carbon particles in healthy subjects and subjects with asthma. *Res Rep Health Eff Inst* 2004;126:1–47.
17. Huang YC, Rappold AG, Graff DW, et al. Synergistic effects of exposure to concentrated ambient fine pollution particles and nitrogen dioxide in humans. *Inhal Toxicol* 2012;24(12):790–7.

18. Li XY, Brown D, Smith S, et al. Short-term inflammatory responses following intra-tracheal instillation of fine and ultrafine carbon black in rats. *Inhal Toxicol* 1999; 11(8):709–31.
19. Oberdörster G, Ferin J, Lehnert BE. Correlation between particle size, in vivo particle persistence, and lung injury. *Environ Health Perspect* 1994;102(Suppl 5): 173–9.
20. Gauderman WJ, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;351(11):1057–67.
21. Rundell KW. Pulmonary function decay in women ice hockey players: is there a relationship to ice rink air quality? *Inhal Toxicol* 2004;16(3):117–23.
22. Rundell KW, Spiering BA, Evans TM, et al. Baseline lung function, exercise-induced bronchoconstriction, and asthma-like symptoms in elite women ice hockey players. *Med Sci Sports Exerc* 2004;36(3):405–10.
23. Rundell KW, Spiering BA, Baumann JM, et al. Bronchoconstriction provoked by exercise in a high-particulate-matter environment is attenuated by montelukast. *Inhal Toxicol* 2005;17(2):99–105.
24. Rundell KW, Caviston R, Hollenbach AM, et al. Vehicular air pollution, playgrounds, and youth athletic fields. *Inhal Toxicol* 2006;18(8):541–7.
25. Schwartz J, Neas LM. Fine particles are more strongly associated than coarse particles with acute respiratory health effects in schoolchildren. *Epidemiology* 2000;11(1):6–10.
26. McCreanor J, Cullinan P, Nieuwenhuijsen MJ, et al. Respiratory effects of exposure to diesel traffic in persons with asthma. *N Engl J Med* 2007;357(23):2348–58.
27. Bernard A. Chlorination products: emerging links with allergic diseases. *Curr Med Chem* 2007;14(16):1771–82.
28. Rundell KW. High levels of airborne ultrafine and fine particulate matter in indoor ice arenas. *Inhal Toxicol* 2003;15(3):237–50.
29. Mannix ET, Farber MO, Palange P, et al. Exercise-induced asthma in figure skaters. *Chest* 1996;109(2):312–5.
30. 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.
31. Hollenbach AM, Caviston R, Rundell KW. Exercise while breathing high ambient auto/truck emission causes decreased lung function in non-asthmatic subjects. *Med Sci Sports Exerc* 2007;39(5):S323.
32. Freed AN, Omori C, Schofield BH, et al. Dry air-induced mucosal cell injury and bronchovascular leakage in canine peripheral airways. *Am J Respir Cell Mol Biol* 1994;11:724–32.
33. Omori C, Schofield BH, Mitzner W, et al. Hyperpnea with dry air causes time-dependent alterations in mucosal morphology and bronchovascular permeability. *J Appl Physiol* 1995;78(3):1043–105.
34. Davis MS, Schofield B, Freed AN. Repeated peripheral airway hyperpnea causes inflammation and remodeling in dogs. *Med Sci Sports Exerc* 2003;35:608–16.
35. Chimenti L, Morici G, Paternò A, et al. Endurance training damages small airway epithelium in mice. *Am J Respir Crit Care Med* 2007;175(5):442–9.
36. 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;166:878–82.
37. Davis MS, Williams CC, Meinkoth JH, et al. Influx of neutrophils and persistence of cytokine expression in airways of horses after performing exercise while breathing cold air. *Am J Vet Res* 2007;68:185–9.
38. Davis MS, Malayer JR, Vandeventer L, et al. Cold weather exercise and airway cytokine expression. *J Appl Physiol* 2005;98:2132–6.

39. Broeckaert F, Arsalane K, Hermans C, et al. Serum Clara cell protein: a sensitive biomarker of increased lung epithelium permeability caused by ambient ozone. *Environ Health Perspect* 2000;108:533–7.
40. Bolger C, Tufvesson E, Sue-Chu M, et al. Hyperpnoea-induced bronchoconstriction and urinary CC16 levels in athletes. *Med Sci Sports Exerc* 2000;43:1207–13.
41. Bolger C, Tufvesson E, Anderson SD, et al. Effect of inspired air conditions on exercise-induced bronchoconstriction and urinary CC16 levels in athletes. *J Appl Physiol* 2011;111:1059–65.
42. Barraza-Villarreal A, Sunyer J, Hernandez-Cadena L, et al. Air pollution, airway inflammation, and lung function in a cohort study of Mexico City schoolchildren. *Environ Health Perspect* 2008;116(6):832–8.
43. Cho WS, Choi M, Han BS, et al. Inflammatory mediators induced by intratracheal instillation of ultrafine amorphous silica particles. *Toxicol Lett* 2007;175(1–3):24–33.
44. Donaldson K, Tran CL. Inflammation caused by particles and fibers. *Inhal Toxicol* 2002;14(1):5–27.
45. Larsson BM, Sehlstedt M, Grunewald J, et al. Road tunnel air pollution induces bronchoalveolar inflammation in healthy subjects. *Eur Respir J* 2007;29(4):699–705.
46. Rundell KW, Slee JB, Caviston R, et al. Decreased lung function after inhalation of ultrafine and fine particulate matter during exercise is related to decreased total nitrate in exhaled breath condensate. *Inhal Toxicol* 2008;20(1):1–9.
47. Zielinski H, Mudway IS, Bérubé KA, et al. Modeling the interactions of particulates with epithelial lining fluid antioxidants. *Am J Physiol* 1999;277:L719–26.
48. Al-Humadi NH, Siegel PD, Lewis DM, et al. Alteration of intracellular cysteine and glutathione levels in alveolar macrophages and lymphocytes by diesel exhaust particle exposure. *Environ Health Perspect* 2002;110(4):349–53.
49. Islam T, Berhane K, McConnell R, et al. Glutathione-S-transferase (GST) P1, GSTM1, exercise, ozone and asthma incidence in school children. *Thorax* 2009;64(3):197–202.
50. Souza MB, Saldiva PH, Pope CA 3rd, et al. Respiratory changes due to long-term exposure to urban levels of air pollution: a histopathologic study in humans. *Chest* 1998;113(5):1312–8.
51. Pinkerton KE, Green FH, Saiki C, et al. Distribution of particulate matter and tissue remodeling in the human lung. *Environ Health Perspect* 2000;108(11):1063–9.
52. Calderón-Garcidueñas L, Mora-Tiscareño A, Fordham LA, et al. Respiratory damage in children exposed to urban pollution. *Pediatr Pulmonol* 2003;36(2):148–61.
53. Salvi S, Blomberg A, Rudell B, et al. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. *Am J Respir Crit Care Med* 1999;159(3):702–9.
54. Nightingale JA, Maggs R, Cullinan P, et al. Airway inflammation after controlled exposure to diesel exhaust particulates. *Am J Respir Crit Care Med* 2000;162(1):161–6.
55. Ercan H, Birben E, Dizdar EA, et al. Oxidative stress and genetic and epidemiologic determinants of oxidant injury in childhood asthma. *J Allergy Clin Immunol* 2006;118(5):1097–104.
56. Zaman K, Hanigan MH, Smith A, et al. Endogenous S-nitrosoglutathione modifies 5-lipoxygenase expression in airway epithelial cells. *Am J Respir Cell Mol Biol* 2006;34(4):387–93.
57. Rabinovitch N, Strand M, Gelfand EW. Particulate levels are associated with early asthma worsening in children with persistent disease. *Am J Respir Crit Care Med* 2006;173(10):1098–105.

58. Hyseni X, Soukup JM, Huang YC. Pollutant particles induce arginase II in human bronchial epithelial cells. *J Toxicol Environ Health A* 2012;75(11):624–36.
59. Meurs H, Maarsingh H, Zaagsma J. Arginase and asthma: novel insights into nitric oxide homeostasis and airway hyperresponsiveness. *Trends Pharmacol Sci* 2003;24(9):450–5.
60. Dai J, Xie C, Vincent R, et al. Air pollution particles produce airway wall remodeling in rat tracheal explants. *Am J Respir Cell Mol Biol* 2003;29(3 Pt 1):352–8.
61. 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.
62. Rundell KW, Spiering BA, Judelson DA, et al. Bronchoconstriction during cross-country skiing: is there really a refractory period? *Med Sci Sports Exerc* 2003;35:18–26.
63. Pohjantähti H, Laitinen J, Parkkari J. Exercise-induced bronchospasm among healthy elite cross country skiers and non-athletic students. *Scand J Med Sci Sports* 2005;15(5):324–8.
64. Sue-Chu M, Brannan JD, Anderson SD, et al. Airway hyperresponsiveness to methacholine, adenosine 5-monophosphate, mannitol, eucapnic voluntary hyperpnoea and field exercise challenge in elite cross-country skiers. *Br J Sports Med* 2010;44(11):827–32.
65. Larsson K, Ohlsén P, Larsson L, et al. High prevalence of asthma in cross country skiers. *BMJ* 1993;307(6915):1326–9.
66. Stenfors N. Self-reported symptoms and bronchial hyperresponsiveness in elite cross-country skiers. *Respir Med* 2010;104(11):1760–3.
67. Helenius I, Haahtela T. Allergy and asthma in elite summer sport athletes. *J Allergy Clin Immunol* 2000;106(3):444–52.
68. 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(5):722–6.
69. 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.
70. Sue-Chu M. Winter sports athletes: long-term effects of cold air exposure. *J Sports Med* 2012;46(6):397–401.
71. Bernard A, Nickmilder M, Voisin C. Outdoor swimming pools and the risks of asthma and allergies during adolescence. *Eur Respir J* 2008;32(4):979–88.
72. Bougault V, Boulet LP. Airway dysfunction in swimmers. *Br J Sports Med* 2012;46(6):402–6.
73. Helenius I, Ryttilä P, Sarna S, 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. *J Allergy Clin Immunol* 2002;109(6):962–8.
74. Castricum A, Holzer K, Brukner P, et al. The role of the bronchial provocation challenge tests in the diagnosis of exercise-induced bronchoconstriction in elite swimmers. *Br J Sports Med* 2010;44(10):736–40.
75. Beuther DA, Martin RJ. Efficacy of a heat exchanger mask in cold exercise-induced asthma. *Chest* 2006;129(5):1188–93.