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Prevalence and Mechanisms of Development of Asthma and Airway Hyperresponsiveness in Athletes

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Abstract

A high prevalence of asthma and airway hyperresponsiveness (AHR) has been reported in the athlete population. Factors potentially predisposing athletes to these conditions have not been clearly identified. Although moderate exercise has been shown to be beneficial in patients with asthma, repeated high-intensity exercise could possibly contribute to the development of asthma and AHR. This report provides an overview of the prevalence and possible mechanisms of development of asthma and AHR in the athlete population. The prevalence of asthma and AHR are higher in athletes than in the general population, particularly in swimmers and athletes performing sports in cold air environments. Possible mechanisms involved in the development of asthma in athletes are still uncertain;

however, the content and physical characteristics of the inhaled air seem to be important factors, while immune and neurohumoral influences could play a modulatory role. This report stresses the need for further studies to better define the aetiologic factors and mechanisms involved in the development of asthma and AHR in athletes, and proposes relevant preventive and therapeutic measures.

Asthma is a common disease, affecting from 5 to 10% of the population.^[1,2] Its prevalence has increased over the last 2 decades, and the causes of this increase are uncertain.^[3,4] Asthma is also commonly found in athletes.^[5,6] Physical exertion frequently triggers asthma symptoms in athletes who already have asthma, as well as in nonathletes.^[7,8] Furthermore, recent observations suggest that high-level exercise performed on a regular basis might contribute to the development of asthma in athletes previously unaffected by the disease.^[5,9] In this review, we will discuss the influence of exercise on the respiratory system, particularly on asthmatic airways, and review the current evidence that high-level exercise may be involved in the development of asthma in athletes.

1. Asthma and Airway Hyperresponsiveness (AHR)

1.1 Asthma

The American Thoracic Society^[10] defines asthma as a clinical syndrome characterised by an increased response of the trachea and bronchi to a variety of stimuli. The main symptoms, episodes of dyspnoea, wheezing and cough, can range from mild and intermittent to severe and continuous.^[10] In 1997, the National Heart, Lung and Blood Institute published their guidelines^[11] for the diagnosis and management of asthma and qualified asthma as a chronic inflammatory disorder of the airways where many cells and cellular elements, in particular, mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils and epithelial cells, play a significant role. In individuals susceptible to developing asthma, inflammation can cause recurrent episodes of wheezing, breathlessness, chest tightness and cough, particularly at night or in the morning. These episodes are usually associated with a variable airflow ob-

struction and are often reversible, either spontaneously or following a treatment with bronchodilators or corticosteroids. The main elements of asthma definition, therefore, include variable airflow obstruction, airway hyperresponsiveness (AHR) and airway inflammation.^[12] Asthma is considered to have a major genetic component, but its development seems in most instances to be determined by environmental exposure, such as to airborne allergens to which the individual is sensitised.

1.2 AHR

Airway responsiveness is the normal tendency for airways to constrict under the influence of non-sensitising physical stimuli such as cold air and exercise, chemical substances such as methacholine and histamine, or sensitising agents such as allergens, in sensitised individuals.^[13,14] AHR could then be defined as the increase above normal in the degree to which the airways will constrict upon exposure to these stimuli. When measured with histamine or methacholine, this increased response is manifested by both the ease of airway narrowing, as shown by a left shift of the dose-response curve, and the magnitude of airway constriction expressed by an elevation and eventually the loss of the maximal plateau response.^[15] AHR may be observed in asymptomatic individuals and some patients with asthma may have normal airway responsiveness when not exposed to a relevant sensitising agent (e.g. seasonal asthma).^[14] Although symptomatic asthma is typically associated with AHR, this may be observed without clinical manifestations.

1.3 Inflammation and Remodelling

Inflammation is a nonspecific response of tissues to injury which usually leads to repair and restoration of the normal structure and function.

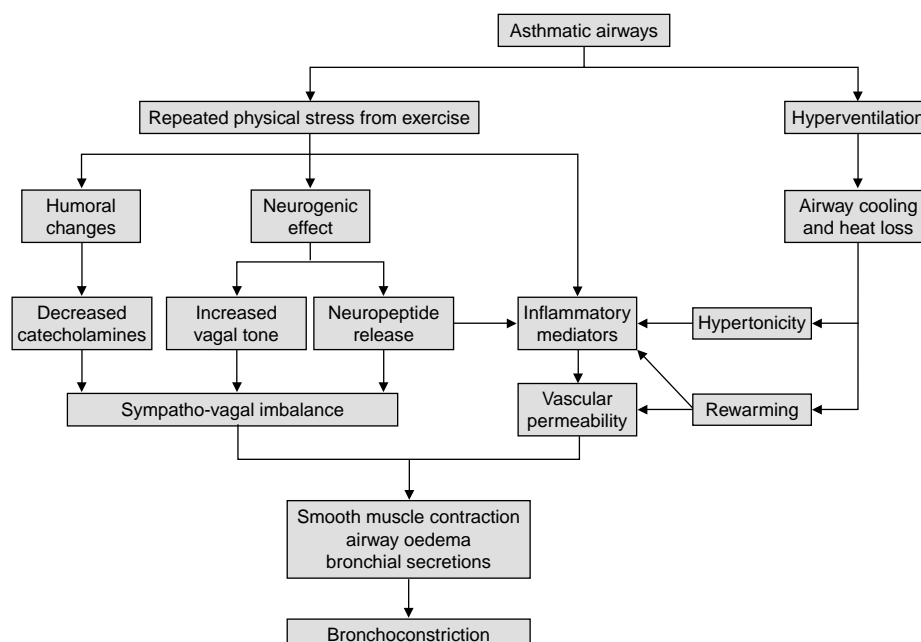


Fig. 1. Effect of exercise in athletes with asthma.

With asthma, however, airway inflammation is chronic, and is associated with a continual or abnormal healing process resulting in structural alterations referred to as 'airway remodelling.'^[16,17] This remodelling process is characterised by various changes such as hypertrophy and hyperplasia of airway smooth muscle,^[18] increased numbers of mucous glands,^[19] thickening of the reticular basement membrane from collagen deposition,^[20] blood vessel proliferation,^[21] and alterations of the extracellular matrix.^[22] This whole process may lead to airway wall thickening and a permanent reduction in airway calibre.^[23]

2. Effects of Exercise in Individuals with Asthma

Exercise-induced asthma (EIA) is defined as an intermittent narrowing of airways generally occurring about 5 to 15 minutes after intense exercise of variable duration. It is characterised by respiratory symptoms such as wheezing, dyspnoea, chest tightness and cough.^[24,25] The definitive diagnosis of

EIA is confirmed by the measurement of pre- and post-exercise expiratory flows documenting either a 15% fall in the forced expiratory volume in 1 second (FEV₁), or a ≥ 15 to 20% fall in peak expiratory flow (PEF).^[26] It is estimated that EIA affects between 40 and 90% of all patients with asthma.^[7,27] In those so affected, the physical stress and the associated hyperventilation caused by an exercise-induced demand for gas exchange leads to a series of events that promotes bronchoconstriction (fig. 1). The ease with which one develops exercise-induced bronchoconstriction may correlate with the severity of asthma and to its degree of control; Asthma Consensus Guidelines include exercise tolerance as a criterion of asthma control.^[28]

2.1 Mechanisms of Development of Exercise-Induced Asthma

2.1.1 Airway Cooling and Hydrocaloric Loss

In 1977, Chen and Horton^[29] suggested that hyperventilation could induce a bronchoconstriction due to cooling and water vapour loss from the air-

ways. When physical exercise induces hyperventilation, a large part of the cooling of the bronchial mucosa is associated with a vaporisation phenomenon required to humidify and warm the inhaled air. This cooling of the airways is directly related to the transfer of heat from the mucosa to the circulating air of the bronchial tree (respiratory heat exchange).^[30] As it is physically impossible to evaporate water from a surface without reducing its temperature, it may not be possible to physiologically dissociate the evaporation of water from the cooling of the airways.^[31] This phenomenon combining heat and water loss seems to be the first in a series of steps leading to the bronchoconstriction response.^[32]

2.1.2 Hyperosmolarity

Anderson et al.^[33] proposed that water loss in the airways could contribute to EIA through the development of a hypertonicity of the liquid at the surface of the airways. The water loss induced by exercise creates a transient dehydration of the bronchial mucosa.^[31] This would lead to a hyperosmolarity of the mucosal fluid that could activate mast cells through the osmotic gradient and promote the release of certain pro-inflammatory mediators or activate cholinergic receptors,^[3,34] resulting in airway events such as constriction of bronchial smooth muscle.^[35] These inflammatory mediators include histamine, prostaglandins, leukotrienes and neutrophil chemotactic factors, and although their effects have been widely studied, their exact role in EIA remains to be defined.^[32,35-37] The precise mechanism of EIA induction is uncertain, and the consequences of exercise-induced airway dehydration remains to be further explored.^[38]

2.1.3 Airway Rewarming

McFadden and colleagues^[39,40] hypothesised that the rewarming of the airways following exercise could also contribute to EIA. This airway rewarming is a physiological consequence of the airway cooling and water loss during exercise. The excess heat generated by the pulmonary circulation necessary to cool the body would lead to a vasodilatation of the pulmonary capillary causing a vascular bronchial congestion. The increased bronchial

vascular permeability and resulting oedema would contribute further to the bronchoconstriction.^[30,31] However, the fact that bronchoconstriction may sometimes begin even before the end of exercise goes against this hypothesis, although it could worsen the bronchoconstriction induced by stimuli such as the dehydration of airways.^[30]

2.2 Influence of Regular Exercise on Asthma Control

Moderate regular exercise has been shown to be beneficial in the control of asthma.^[41] In patients with asthma, physical training may increase the maximal oxygen uptake ($\dot{V}O_{2max}$) to the same degree as healthy individuals without asthma.^[42] Rasmussen et al.^[43] conducted a longitudinal study to determine whether achieving good physical condition could have some protective effect against the development of asthma in adolescents. They investigated 1369 schoolchildren (mean age: 9.7 years) and proceeded to a 10.5-year follow-up to find an inverse relationship between physical fitness and the risk of developing asthma.

Athletes with mild to moderate asthma can develop a high degree of endurance fitness and a high $\dot{V}O_{2max}$ during an endurance event.^[44] Freeman et al.^[45] compared a group of asthmatic and nonasthmatic athletes before, during and after 2 hours on a treadmill at 70% of $\dot{V}O_{2max}$ to observe no significant differences in their metabolic and cardiorespiratory responses; they concluded that athletes with asthma adapt to their limitations. In the nonasthmatic group, increased ventilation was achieved by an increase in the breathing frequency, while tidal volume was reduced. In asthmatic athletes, increased ventilation resulted from a smaller increase in breathing frequency with an unchanged tidal volume. According to these authors, the maintenance of the tidal volume by athletes with asthma during endurance sport events could compensate for the development of airflow obstruction and allow them to perform successfully, although other mechanisms may be involved.

3. Prevalence of Asthma and AHR Among Athletes

The physiopathology of EIA has been thoroughly studied, but the long term respiratory effects of intense exercise or exercise carried out in extreme environmental conditions remain to be explored. Exercise may induce a beneficial effect on the control of asthma when practised at mild to moderate levels and in usual conditions.^[43,46] As demonstrated for other systems, however, it is possible that very intense and repeated exercise, particularly when performed over many years, could cause respiratory health problems. A recent evaluation of different types of athletes suggested that there is an increased prevalence of lower airway diseases, particularly asthma, in high-level athletes.

Weiler et al.^[6] have reported that 15.3% of the 699 athletes taking part to the 1996 Summer Olympic Games who agreed to complete a questionnaire reported having a previous diagnosis of asthma. In 1998, the same authors observed a prevalence of 21.9% in 196 Winter Game Olympic athletes using the same criteria.^[47] After the 1984 Summer Olympic Games, Pierson and Voy^[48,49] reported that 11% of 597 athletes participating in the games had EIA. These figures may underestimate the prevalence of asthma and suggest under-diagnosis of this condition in athletes. In this regard, Kukafka et al.^[50] studied 238 football players and reported that 24 (10%) of them had a history of treated asthma. However, among the remaining 214 athletes, 19 (9%)

had EIA defined as a decrease of 15% in PEF post-exercise.

Table I illustrates the prevalence of physician-diagnosed asthma, EIA and AHR reported by different investigators. Since the development of these conditions in athletes is possibly caused by different mechanisms (as suggested in a recent report),^[9] studies on the prevalence of physician-diagnosed asthma, EIA and AHR were classified according to 3 different training environments: those training in cold air, swimmers training in indoor-pools and those training mainly in ambient dry air.

The prevalence of diagnosed asthma reported in athletes exercising in cold air ranged from 14 to 28%.^[9,47,51] Although various methods were used to evaluate EIA, its prevalence was 23 to 35%^[52-55] and for AHR, 23 to 52%.^[9,56,57]

For athletes practising in indoor swimming pools, the prevalence of reported AHR was quite high. Studies in competitive swimmers found a prevalence of AHR ranging from 36 to 79%; this was significantly higher than controls.^[5,9,587-60] Surprisingly, the prevalence of physician-diagnosed asthma for swimmers in the study of Langdeau et al.^[9] was only 8%.

For other sports including various athletes such as sprinters, long-distance runners, football players, basketball players and other track and field athletes, the prevalence of physician-diagnosed asthma, EIA and AHR was more homogeneous and usually ranged from 8 to 21%.^[5,9,48,49,56,61,62,64,65]

Table I. Prevalence of physician-diagnosed asthma, exercise-induced asthma and airway hyperresponsiveness (AHR)

	Physician-diagnosed asthma	Exercise-induced bronchoconstriction	AHR to methacholine or other agents
Athletes training in cold air environment	28% ^{a[9]} , 22% ^[47] , 14% ^{a[51]}	23% ^[52] , 31% ^[53] , 35% ^[54] , 30% ^[55]	35% ^[56] , 52% ^{a[9]} , 23% ^[57]
Swimmers	8% ^{b[9]}		76% ^{a[9]} , 36% ^{a[5]} , 48% ^{a[58]} , 60% ^{a[59]} , 79% ^{a[60]}
Others	20% ^[9] , 17% ^{ac[61]} , 8% ^{bd[61]} , 11% ^[49] , 9% ^[62] , 2% ^{b[63]}	15% ^[64] , 19% ^[65]	21% ^[56] , 9% ^{bc[5]} , 18% ^{ad[5]} , 14% ^[48]

a Studies using controls showing prevalence significantly different than the athletes.

b Studies using controls showing prevalence not significantly different than the athletes.

c Long-distance runners.

d Sprinters.

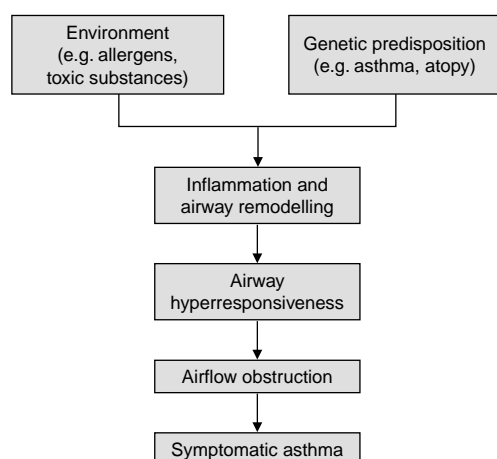


Fig. 2. Development of asthma in the general population.

Among the reports on the prevalence of asthma or AHR in athletes, few showed no increase in prevalence compared with the general population. Kujala et al.^[63] retrospectively analysed 1282 former elite athletes from Finland who participated in at least 1 international competition between 1920 and 1965, as well as a nonathlete control group (n = 777) and found that asthma prevalence was no higher in individuals with a past history of participation in athletic competition. It is not clear why these observations differ from more recent studies.

4. Mechanisms Possibly Contributing to the Development of Asthma in Athletes

In the general population, the development of asthma is considered to be of multifactorial origin, and environmental factors such as exposure to pro-inflammatory substances in susceptible individuals may contribute to the development of this disease (fig. 2).^[66] In particular, atopy and indoor allergen exposure have been related to asthma.^[67] There is increasing evidence suggesting that asthma is a disorder with a major genetic component, often associated with atopy.^[68] A child born into a family with one or more members with asthma and/or with atopy has a greater risk of developing asthma.^[69,70] Furthermore, the environment can contribute di-

rectly to the development of asthma or act as an amplifying factor in predisposed individuals or those already with asthma.^[71-74]

4.1 Role of Exercise-Induced Increase in Ventilation and Influence of Inhaled Air Content

It has been suggested that the characteristics of inhaled air during exercise could be a contributing factor in the development of AHR among athletes (fig. 3).^[8,30] Obviously, depending on the sport practised, athletes evolve in a variety of environments where the characteristics of the inhaled air may indeed predispose them to the development of AHR. Hyperventilation exposes the airways to different substances such as allergens, particles or pollutants in suspension in the air. Furthermore, hyperventilation implies some indirect effects that could also contribute to the development of asthma in athletes.

4.1.1 Mechanical Effects

The possibility that sustained mechanical stress to the airways during marked hyperventilation could affect airway function is supported by studies on mechanical ventilation, suggesting that such airway stress could induce a local inflammatory process.^[75,76] However, more studies should be done to determine whether repeated mechanical stimuli to the airways can induce permanent structural and/or physiological changes.

4.1.2 Inhaled Air Content and Airway Inflammation/Remodelling

Cold air

Exposure to cold air is certainly one of the most studied conditions potentially influencing the development of asthma among athletes. It is uncertain whether the bronchoconstrictive response to cold air is the effect of the low temperature itself or of the low water content of that inhaled air, although both factors may contribute.^[8,77] Furthermore, intense exposure to cold air could possibly create sufficient epithelial damage and inflammation to modify airway function.

Larsson et al.^[77] proposed that exposure to cold air could promote airway inflammation by inducing an influx of cells and mediators in the lower airways of healthy individuals without asthma. These authors found that after a period of exposure to cold air (-23°C) the bronchoalveolar lavage fluid of healthy individuals presented a number of granulocytes and alveolar macrophages significantly higher than that found after comparable exposure to normal indoor air (22°C). Sue-Chu et al.^[78] observed the presence of lymphoid aggregates in endobronchial biopsies of both skiers and controls but the frequency of these aggregates was 2.5 times greater in skiers (64%) than in controls (25%). Furthermore, lymphoid aggregates were seen more frequently in skiers using β_2 -agonists and with AHR to methacholine.

Recent publications are particularly enlightening on this subject. Firstly, Sue-Chu et al.^[79] showed mild to moderate airway inflammation of proximal airways in adolescent cross-country skiers, with an increase in the percentage of lymphocytes and mast

cells in bronchoalveolar lavage fluid. Karjalainen et al.^[80] studied 40 competitive cross-country skiing athletes from Sweden and Norway without a diagnosis of asthma, compared with 12 individuals with mild asthma and 12 nonathletic controls. On bronchial biopsies, the skiers had a significant increase in airway T-lymphocyte, macrophage and eosinophil counts compared with the normal controls, although it was less marked than in individuals with asthma. Neutrophil counts were more than 2-fold greater in skiers than in patients with asthma. The expression of an extracellular matrix protein, tenascin, was increased in the airway epithelium basement membrane area in both skiers and individuals with asthma, and did not correlate with inflammatory cell counts. All abnormalities were more marked in skiers with AHR than in those with normal airway responsiveness. This is in keeping with some of our previous observations in individuals with asymptomatic AHR.^[81]

This study suggests that an inflammatory process could be triggered by repeated exposure of

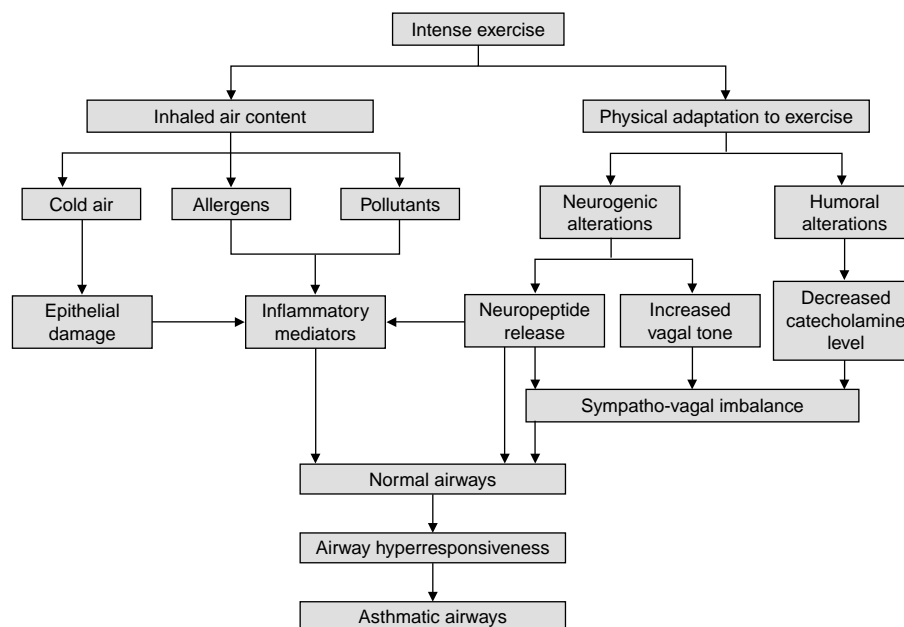


Fig. 3. Development of asthma in athletes.

proximal airways to inadequately conditioned air. This is also in keeping with studies on animal models, where hyperventilation with dry air at room temperature was associated with epithelial injury and leucocyte airway infiltration.^[82] Furthermore, changes in airway tenascin may indicate that the airways of these athletes show an increased healing and repair process.

Allergens

The association between atopy and asthma is largely recognised.^[83,84] More than 70% of individuals with asthma have at least 1 positive skin reaction to skin-prick tests with common airborne allergens.^[85] Scant data are available, however, on the contribution of allergens to the development of AHR in the athlete population.^[62]

Kaelin and Brändli^[86] administered a questionnaire on allergy and respiratory symptoms related to exercise to 1530 Swiss athletes at national and international levels. This study showed a significant correlation between atopy and respiratory symptoms. The analysis of a subgroup of 104 responders made it possible to observe a correlation between the number of positive responses to skin-prick tests and a reduction in FEV₁ after a 10-minute exercise on a stationary ergometer.

Helenius et al.^[61] also found that the incidence of atopy was higher in athletes and suggested that this phenomenon could result from periods of prolonged hyperventilation following intense exercise, increasing exposure to different allergens or irritants inhaled during training or competition. The increased allergen load to the airways could therefore, through an immunoglobulin E (IgE)-dependent mechanism, induce an inflammatory process that might contribute to the development of AHR.^[87]

Pollutants

For athletes who train outdoors, the quality of the inhaled air varies and the presence of different pollutants may contribute to the development of AHR. In industrialised cities, among many identified pollutants, such as sulphur dioxide (SO₂), nitrogen dioxide (NO₂) and others, ozone (O₃) is by far the most studied substance.^[88-90] In asthmatic as well as healthy individuals without asthma, ex-

posure to a weak concentration of ozone (0.15 ppm) induces a neutrophilic airway inflammation and increases many other inflammatory mediators in the airway.^[91] Several studies have demonstrated that the combination of exercise and exposure to such pollutants as SO₂ and ozone can cause a significant increase in bronchoconstriction and a reduction in ventilatory flow when compared with pollution exposure at rest.^[92,93] There is also evidence that a daily exposure to ozone leads to the development of tolerance to this substance in both individuals with asthma and controls.^[94,95]

Pollution may only affect some categories of athletes and not be relevant in others. With regard to the effect of outdoor pollution on airways, although it may sometimes increase symptoms, it does not seem to be a major factor in the development of asthma.^[96] However, the situation can be different for indoor pollution, and there are data that pollutants could be a co-factor enhancing allergen-induced airway inflammation.^[97]

For athletes who practice their sport in indoor arenas, the exposure to such contaminants as carbon monoxide (CO), nitric oxide (NO), NO₂ and a variety of organic volatile compounds could contribute to certain respiratory problems, such as AHR.^[98,99] On the other hand, the potential risks associated with this type of exposure are still being debated.^[88,89]

The inhalation of humid air can reduce the bronchoconstrictor response to exercise.^[30,100] However, an increasing number of authors reporting abnormally high prevalence of AHR among swimmers^[9,59,60] suggests that the environment of certain indoor swimming pools promotes the development of AHR in athletes. Recent studies have proposed that indoor air in swimming pool environments contains chemical compounds used for water treatment such as chlorine and its derivatives, chloramine and chloroform, which could act as irritants to the airways.^[59]

Helenius et al.^[58] used induced sputum analysis in 29 elite swimmers and 19 healthy controls to investigate the long term effects of training on airway inflammation in swimmers. They found that eosinophil and neutrophil counts in sputum were

significantly higher in swimmers than in controls. Furthermore, symptomatic swimmers had significantly more sputum eosinophils than symptom-free swimmers. It has been proposed that long term repeated exposure to chlorine-compound derivatives could be contributing to the observed airway inflammation in elite swimmers.^[101]

Airway inflammation may cause or increase AHR (fig. 3).^[102] It is therefore possible that the higher prevalence of asthma in athletes performing in certain environments may be caused by a chronic inflammatory/remodelling process in the airways triggered by allergens or irritants inhaled in large quantities.

4.2 Immune System Changes

Increasing evidence suggests that intense exercise causes a certain degree of immunodepression and an increased susceptibility to infections.^[103-105] On the other hand, no clear evidence has yet surfaced linking exercise, the immune system and asthma. Immune system response to exercise is largely dependent on the intensity level of the effort generated.^[106,107] A light- to moderate-intensity exercise induces a favourable immune system response. In contrast, following an intense session, the high level of prostaglandins produced by the elevated number of blood monocytes inhibits the natural killer cell function suggesting that it may impair the immune response.^[108] Other authors have also observed an increase in blood monocytes and macrophages in response to an intense physical effort.^[105]

The effects of intense repeated exercise on the immune system may include: suppression of lymphocyte production, suppression of neutrophil function, a decrease of the antiviral properties of macrophages and natural killer cell activity, as well as diminution of lymphokines and IgA levels. All these effects have been observed at the site of the respiratory mucosa.^[106,109,110] Furthermore, many of these immunological alterations persist for hours or even days, following intense exercise.^[111]

An epidemiological study by Nieman^[112] suggested that athletes practising 'endurance'-type training had an increased risk of upper respiratory tract

infection. This author, evaluating athletes who took part in the 1987 Los Angeles marathon, found that 40% of the runners reported at least 1 episode of upper respiratory tract infection during the 2-month period preceding the competitive event (known to be an intense training period), and that 13% reported at least 1 episode during the week following the event, compared with 2.2% among the control runners who did not participate in the event.^[103]

Davis et al.^[113] demonstrated that intense exercise lowers antiviral resistance while raising susceptibility to respiratory infections. Susceptibility to upper respiratory tract infection increased in over-trained athletes.^[114] An association was also observed between a transient increase in AHR and respiratory tract infection among athletes during periods of intense training.^[115]

4.3 Neurohumoral Influences

4.3.1 Parasympathetic Hyperactivity

In contrast to other systems of the human body which have both sympathetic (adrenergic) and parasympathetic (cholinergic) innervation, the predominant innervation at the bronchial level is parasympathetic in nature.^[116] The parasympathetic system plays an important role in the regulation of airway tone and bronchial secretory activity. The airway smooth muscle receives neural innervation by a network of efferent parasympathetic fibres.^[117,118] In humans, however, it has been demonstrated by histochemistry that the sympathetic (adrenergic) innervation is rather sparse. The very few sympathetic fibres identified in human airways are in close association with submucosal gland bronchial arteries.^[118]

The balance between the sympathetic and parasympathetic activity is very complex. Mechanisms of modulation of bronchial tone and their possible role in the development of AHR need to be further investigated. However, certain observations suggest the presence of a correlation between parasympathetic activity and AHR (fig. 3).^[119,120]

Given that the parasympathetic system modulates airway tone, it is logical to suppose that hyperactivity of that system would produce an in-

crease in basal bronchomotor tone and contribute to a greater likelihood of developing AHR. The analysis of 'respiratory sinus arrhythmia' provides a valuable method of measuring cardiac vagal efferent activity.^[121] Kallenbach et al.^[119] used this method to investigate the possibility that an increase in parasympathetic activity could contribute to AHR. Since the rate of discharge of the sinoatrial node is modulated by the vagus nerve, it is conceivable that a change in the control of heart rate reflects a parallel activity of vagal tone on the airways. These investigators observed a strong correlation ($r = 0.70$, $p < 0.005$) between AHR and parasympathetic activity in 15 individuals with asthma, whereas no correlation was found in 18 nonasthmatic controls. They concluded that individuals with asthma have a higher level of parasympathetic activity than those without asthma, supporting the hypothesis that enhanced parasympathetic activity is a significant factor in the pathogenesis of bronchial asthma.

With regard to the possible involvement of parasympathetic activity in AHR, athletes have a higher parasympathetic tone than healthy sedentary individuals. Goldsmith et al.^[122] assessed the level of parasympathetic activity of trained individuals without asthma ($\dot{V}O_{2\max} \geq 55$ ml/min/kg) compared with untrained individuals without asthma ($\dot{V}O_{2\max} \leq 40$ ml/min/kg) by calculating the high frequency of the heart rate variability of a 24-hour ECG recording. Parasympathetic activity was substantially greater in trained individuals. Using the respiratory sinus arrhythmia method, De Meersman^[123] also observed an increase in efferent parasympathetic activity in trained runners after an 8-week high-intensity running programme.

It is reasonable to propose that a predominant parasympathetic drive could act as a compensatory response to a prolonged sympathetic stimulation caused by intense and repetitive training periods. This could induce an alteration of the resting cardiac rhythm (bradycardia), a well-known phenomenon,^[124,125] but also an increase in bronchomotor tone and, in turn, an increased susceptibility to the development of AHR.

4.3.2 Catecholamines

Catecholamines are a group of circulating hormones with sympathomimetic action; they include noradrenaline (norepinephrine), adrenaline (epinephrine) and dopamine. Catecholamines mediate sympathetic effects, mostly bronchodilatory, through their affinity with high-density airway β -adrenoceptors.^[118,126,127]

There is heterogeneity among β -adrenoceptors. The β_1 -adrenoceptors have a high affinity for noradrenaline and act in many ways like 'neuronal' receptors while the β_2 -adrenoceptors have a higher affinity for adrenaline and act more like 'hormonal' receptors. In bronchial smooth muscles the density of β_2 -adrenoceptors is significantly higher than that of β_1 -adrenoceptors.^[128] Noradrenaline has very little effect upon the airways,^[129] and acts largely as a neurotransmitter.^[130] However, adrenaline has powerful bronchodilatory effects in both individuals with and without asthma^[131] and has a protective effect against bronchoconstriction. Exercise can induce an increase in catecholamine levels,^[132,133] but the resting baseline values are similar in athletes and nonathletes.^[134,135] Nevertheless, the relationship between circulating catecholamine levels and the development of EIA or the presence of AHR in individuals with asthma remains unclear (fig. 3).^[136-138]

5. Treatment and Preventive Measures

The treatment of asthma aims at achieving optimal control of the disease through patient education, environmental control and individualised pharmacotherapy.

The education of athletes, their families and their coaches is an important component of the non-pharmacological management of asthma.^[139] To demystify asthma, athletes need to be informed that their condition is common among those in high-level competition and will not limit their performance if it is treated adequately. Furthermore, it must be emphasised that the recommended medications do not create addiction, have no or minimal adverse effects when used properly, and will allow them to carry on with regular sports activities and enhance their quality of life. Environmental con-

trol is important, whenever possible. This applies to the home environment of athletes, where avoidance of exposure to relevant allergens and to irritants should be suggested. It also applies to the training environment; for example, better ventilation systems in arenas and indoor pools could possibly help reduce the adverse effects of the numerous contaminants in suspension in the ambient air.

Among the nonpharmacological approaches to EIA, a warm-up period prior to training or sports events can be effective in decreasing the degree of bronchoconstriction through induction of a 'refractory period,' during which airways become less responsive to exercise.^[7,36,140] A 10- to 15-minute warm-up at 60% $\dot{V}O_{2\max}$ can then significantly reduce post-exercise bronchoconstriction in athletes.^[141] Although its exact mechanism is still unknown, refractoriness to bronchoconstriction induced by subsequent exercise challenges can last from 40 minutes up to 3-hours.^[36]

Medication is an important component of asthma therapy in athletes. Inhaled short-acting β_2 -agonists (e.g. salbutamol, fenoterol or terbutaline) taken a few minutes before exercise have protective effects, reducing the degree of bronchoconstriction caused by exercise.^[142,143] Long-acting β_2 -agonists (e.g. salmeterol or formoterol) also provide excellent protection against exercise-induced bronchospasm and their effect can last from 6 to 12 hours after inhalation.^[143,144] However, regular use of long-acting β_2 -agonists to better control asthma in patients with more than mild asthma should always be combined with inhaled corticosteroid use.^[11,28] Finally, it has been found that regular daily use of long-acting β_2 -agonists over a continuous 4-week period is associated with a reduction of its protective effect even with the concomitant use of inhaled corticosteroids.^[145,146]

Although inhaled corticosteroids are the mainstay of asthma therapy,^[28] there are very few studies on the effect of this type of medication in athletes with asthma. In children, there is evidence that the use of corticosteroids in combination with short-acting β_2 -agonists for more than 1 month attenuates the severity of EIA.^[147,148]

There have been some concerns that the use of medications such as inhaled β_2 -agonist bronchodilators could enhance physical performance. However, the many studies performed on athletes, and individuals with and without asthma have demonstrated no significant increase in physical performance with the use of inhaled short- or long-acting β_2 -agonists,^[149-154] inhaled anticholinergics,^[155] or inhaled corticosteroids.^[156]

Antileukotrienes, a new class of asthma medication, show promising potential in asthma management by providing both relieving and controlling effects. Two main types of antileukotriene drugs are currently used: leukotriene receptor antagonists and leukotriene biosynthesis inhibitors. Both have shown beneficial effects in asthma. They have comparable bronchodilator effects, and have been proven to be effective in providing a certain degree of protection against cold air, exercise, and allergen challenges. Their daily use can also improve clinical symptoms and lung function parameters as well as reducing β_2 -agonist and corticosteroid use in some individuals.^[157,158] In recent studies,^[159-161] montelukast and zafirlukast, both leukotriene receptor antagonists, have been shown to antagonise EIA, although generally to a lesser degree than β_2 -agonists.

6. Conclusion

Mild to moderate exercise has beneficial effects on general and respiratory health in those with asthma as well as in individuals without the disease. However, many reports show that elite athletes have a significantly greater prevalence of asthma and AHR than sedentary individuals of the same age group. This prevalence of AHR in athletes seems to vary from one sports discipline to another.

The difference in the prevalence of AHR and asthma between sports disciplines raises the possibility that exercise *per se*, or even repeated maximal ventilatory efforts (hyperventilation), may not be the primary mechanism involved in the development of these conditions in athletes. Environmental factors involving the 'type' and 'content' of the inhaled air could play an important role. Even

if most sports are practised in various air conditions all year long, many sports are predominantly practised either in cold, dry or humid air. The mechanisms involved in the development of AHR and asthma for each of these air categories may be different. Moreover, the exposure to allergens or contaminants in the inhaled air could vary markedly from one sport to another, depending on whether the sport is practised indoors or out, or in one season or another. In athletes practising endurance training, for example, repeated and prolonged periods of hyperventilation expose the airways to numerous respiratory irritants and allergens that can contribute to the development of AHR.

The high prevalence of AHR and asthma in swimmers and other athletes training in indoor pools could be explained by the exposure to chlorine and its derivatives. More efficient ventilation systems in indoor swimming pools and the use of alternative water-disinfecting compounds have the potential to reduce adverse effects on airways. Further studies to explore the causality relationship between indoor pool air contaminants and airway diseases remain to be carried out.

When comparing the prevalence reported for asthma and AHR or EIA, we can observe a higher prevalence of abnormal airway function, in comparison with asthma diagnosis or asthma medication intake. The reasons for this discrepancy are still unknown but this is also a phenomenon observed in the general population, and may be related to the type, speed or perception of physiological changes. Indeed, the presence of AHR or EIA in athletes may not always translate into respiratory symptoms. Temporal adaptation to nociceptive respiratory symptoms may possibly occur in these individuals. Symptoms could also be perceived but tolerated, denied or not interpreted as abnormal or requiring medical assessment. These different aspects of symptom perception in athletes remain to be studied further. This demonstrates that objective measures of airway function in athletes are important and should be emphasised.

It is known that athletes have frequent upper respiratory tract infections and this may increase

the susceptibility to develop asthma. On the other hand, a possible reduction in T helper-2 cell type responses, involved in the development of allergic airway inflammation, may be beneficial in some individuals.^[162] Nevertheless, the possible role of changes in the immune system in the development of asthma in athletes needs to be determined.

With regard to the autonomic nervous system, this does not seem to play a key role in the development of AHR or asthma, but may act as a modulator of airway responses.

The identification of sports associated with a higher risk of developing asthma, better screening procedures and appropriate treatments, and early preventive measures might well produce improved athletic performances among athletes, and would certainly help them achieve a healthier quality of life.

In conclusion, this review emphasises the need to investigate the possible factors that lead to the development of asthma in athletes and the mechanisms involved, and proposes relevant preventive and therapeutic measures.

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