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**Review article**

# Rhinitis and asthma in athletes: an ARIA document in collaboration with GA$^2$LEN

This consensus document is aimed at reviewing evidence that the rhinits-asthma links have peculiar features in athletes. Beside a review of epidemological data on the high prevalence of rhinitis and asthma in athletes, the effects on intense physical exercise on the immune system and repiratory functions are discussed, with special reference to the role of allergens and pollutants. In extending the Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations to athletes, the issue is addressed of adapting diagnosis and management to criteria set by the International Olympic Committee (IOC) and regulations adopted by the World Anti-Doping Agency (WADA).

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Allergic rhinitis and its impact on asthma (ARIA) is an initiative aimed at highlighting the close relationships between rhinitis and asthma on the basis of an evidence-based approach (http://www.whiar.com) (1).

The document has been produced by a WHO expert panel and endorsed by the major allergy/clinical immunology, respiratory and ENT international societies. Translated into several languages it has been diffused worldwide.

Allergic rhinitis and its impact on asthma calls attention, among other issues, on the following:

1 Allergic rhinitis represents a global health problem, affecting 10–25% of the population with a marked effect on economic costs as well as on the quality of life and performances of individuals.
2 Allergic rhinitis, frequently associated with asthma, has close pathophysiological links with it, and represents a risk factor for subsequent development of lower respiratory tract symptoms.
3 Rhinitic subjects should always be evaluated for asthma with adequate history data collection, clinical examination and laboratory tests.

This consensus document is aimed at reviewing evidence that the rhinitis-asthma links have peculiar features in athletes. Extending the ARIA recommendations to elite athletes might have special relevance in view of the World Anti-doping Agency (WADA) regulations as well as of criteria applied by the International Olympic Committee to asthmatic athletes.

## Effects of exercise on the immune system and respiratory functions

In experimental acute models, intense physical exercise is a stress event inducing several changes of immune functions during and after the challenge (2). Changes of immune parameters after exercise include a decrease of neurotrophils, T and B cells with an impaired IgA and IgM production, a reduction of NK cells and an increase of pro-inflammatory cytokines (2). In elite athletes the transient immune-deficiency observed after overtraining is associated with an increased risk of infections, particularly of the upper respiratory tract. The propensity to viral infections as well as to allergic diseases in elite athletes might suggest that strenuous and continuous physical exercise favors a Th1/Th2 unbalance with a prevalent Th2 cytokine profile(3).

Special attention has also been devoted to the effects of physical exercise on the immune system through its effects on neural and endocrine functions (4). The mechanisms by which the neuroendocrine system communicates with the immune system and vice versa have been the object of increasing attention from the scientific community over the past 20 years. The set point of these interactions is determined by the central nervous system through the modulation of hypothalamic–pituitary–adrenal (HPA) axis and the systemic/adrenomedullary sympathetic nervous system (SNS), the peripheral limb of the stress system. Exercise and training activate the central components of the system, the corticotropin-releasing hormone (CRH) and locus ceruleus-norepinephrine/autonomic (sympathetic) neurons which respectively regulate the systemic secretion of glucocorticoids and catecholamines – mainly epinephrine and norepinephrine – which in turn influence the immune responses. The exercise-related stress condition may on the other hand activate another feedback loop in which cytokines produced by immunocompetent cells act on the hypothalamus to regulate the output of glucocorticoids. In particular, tumor necrosis factor (TNF)-$\alpha$, interleukin (IL)-1, and IL-6, may stimulate CRH secretion and activate both the HPA axis and the SNS. Few data are present in the literature concerning the possibility that strenous exercise, by these mechanisms, may interfere in the equilibrium between proinflammatory (IL-12, TNF-$\alpha$, interferon-$\gamma$) and antiinflammatory (IL-10) cytokine production. Catecholamines rapidly released during exercise, through their specific $\beta$2 adrenergic receptor, might upregulate IL-10 production by monocyte/macrophages without affecting the T helper (Th) lymphocyte subclass Th2 directly, even if they may potentiate cytokine production by these cells. Glucocorticoids, released in the delayed response to strenous exercise, through specific cytoplasmatic/nuclear receptors, might upregulate the production of IL-10 and IL-4 by Th2 cells, thus altering the Th1/Th2 balance. Then, hormones released after exercise may exert systemic effects on the pro/antiinflammatory cytokine balance but this evidence may not pertain with local responses in specific compartments of the body. Systemically, exercise-induced release of glucocorticoids and catecholamines seem to be able to stimulate an important immunoendocrine mechanism which protects the athlet from an excessive production of proinflammatory cytokines and other products of activated macrophages with tissue-damaging potential. Locally it may support the cytokine production, suppressing or potentiating the regional immune response [see Warren and Costantini (4) and Khansari et al. (5) for references].

On the other hand, exercise hyperpnea may cause airway obstruction in a number of asthmatic subjects and also marked nasal pathophysiological changes. Interestingly, functional changes of upper and lower airways induced by exercise are accompanied by an increased number of inflammatory cells in the airways and sputum – as described in details below – as well as of circulating CD34 + progenitor cells (6).

## Rhinitis in athletes

Rhinitis occurs very frequently in athletes, its prevalence in various studies depending on the criteria used for

diagnosis. Helbling and Muller (7) found that 16.8% of 2060 active Swiss athletes (of 68 different sports) suffered from hay fever, most of them (59%) needing medication during the pollen season. Athletes with hay fever had significantly more often exercise-related airway symptoms, but received inadequate treatment.

In the study of Katelaris et al. on 214 athletes (8), 56% reported symptoms consistent with allergic rhinoconjunctivitis, 41% also having a positive skin test response to any one allergen and 29% had seasonal allergic conjunctivitis (a positive seasonal history and at least one positive skin prick test response to a seasonal allergen). In another series of 265 athletes selected for the Sydney Olympic Games, the prevalence of positive skin tests was 32.6%, and 25.3% of athletes had clinical rhinitis (3).

As for asthma, the prevalence of allergic rhinitis seems to be on the increase, as the reported prevalence of approximately 8.0% in the 1980s doubled in 1996 (16.9%) (9).

Allergic rhinitis has been shown to have negative effects on performance scores (ability to train and compete). Athletes from aquatic sports were more likely to have symptoms than those from other sports. Athletes who were treated in season with intranasal steroids (once daily, 8 weeks) had statistically significant improvements in symptoms, QoL, and performance scores (10).

### Nasal physiology and pathophysiology during exercise

The nose has two basic functions: olfactory and respiratory. One of its physiologically relevant functions is the conditioning of inspired air, making it suitable for lung gas exchange. This includes the filtration, humidification and warming of inhaled air before it reaches the lower respiratory tract. This conditioning function is mainly dependent on nasal mucosa blood vessels and glands and regulated by autonomic nervous system reflexes (11), which are easily disturbed by the presence of chronic nasal inflammation.

Autonomic reflexes usually improve nasal efficiency during exercise: dynamic exercises, up to a work rate of 120 W, reduce nasal resistance up to 50% of the normal (12), because of an increase in nasal sympathetic tone, causing constriction of nasal blood vessels through $\alpha$-adrenoreceptor stimulation. Isometric exercises produce little nasal effects in normal subjects, but induce a clear increase of nasal resistance in rhinitics. The normal response to standing is also a reduction of nasal resistance, but such response is absent in patients with allergic or nonallergic rhinitis (13). On the other hand, cold air induces glandular hypersecretion and nasal discharge in normal subjects (under parasympathetic control), and this response is increased in severity in rhinitic patients (14).

Furthermore, during regular training athletes are repeatedly exposed to allergens, cold air and pollutants and these can have a significant effect on their allergic diseases and respiratory physiology (15). For instance, the nasal obstruction of rhinitics shifts the pattern of nasal breathing to oral breathing, increasing the exposure of lower airways to allergens, pollutants or other adverse environmental factors. Some studies showed that nasal breathing significantly reduced exercise-induced asthma (16), due to the role of the nose in humidifying inspired air (17).

Although some athletes experience improvement in rhinitis with exercise (through an increase in nasal sympathetic tone), rhinitis may worsen under certain conditions: exposure to allergens (pollens, during outdoor exercise, mites in indoor sports) and inhalation of irritants (ozone, sulphur dioxide or particulates, chlorine derivatives from swimming pools). Athletes may also experience worsening of rhinitis caused by weather conditions, such as cold or dry air. Nasal structural abnormalities, from trauma during sports practice, may also result in rhinitis.

In relation to the type of sports activity, rhinitis may have particular features and pathophysiological mechanisms (see 18 for references).

### Rhinitis in swimmers

Data from the literature show that competitive swimmers, when swimming up to 30 h/week, inhale large amount of air floating just above the water disinfected with either chlorine gas or hypochlorite liquid. These compounds, together with the specific characteristics of the swimming pools water (in term of pH, salt content and temperature) significantly affect the physiological processes of the rhinosinusal district, leading to the development of a typical clinical picture called 'chloride-treated water allergy', characterized by nasal obstruction, watery nasal discharge and sneezing. In a study of 35 elite swimmers it was found that in all of them mucociliary transport was abnormal with a mean value $\pm$ SD of 27.48 $\pm$ 4.94 min (normal value: 13 $\pm$ 3 min), reaching a value of more than 30 min in 10 of these athletes (18). The persistence and stabilization of this kind of alterations certainly expose the swimmers to the development of important disorders such as rhinosinusitis, rhino-otitis and asthma. Moreover, in divers, the repeated sudden changes in pressure at the level of the rhinosinusal district can lead to the development of barotraumatic rhinosinusitis.

### Rhinitis in skiers

Rhinorrhea and nasal congestion after the exposure to cold air is the clinical binomium that characterize the so called 'skier's nose'. Low temperatures play a major role in the genesis of this disorders by acting as a trigger factor for the activation of a parasympathetic reflex which determines in a first phase nasal discharge, followed, in a second phase, by a nasal congestion due to the dilatation of the turbinates vessels. A group of 24 elite skiers of the

Italian Winter Sport Federation underwent active anterior rhinomanometry, acoustic rhinometry and evaluation of mucociliary transport time. Nasal resistance and nasal diameters were determined both in basal conditions and after a nasal decongestant. The study showed that all the above mentioned objective parameters of nasal function were altered in all athletes, being the mean total nasal resistance 0.37 ± 0.05 kPa s/ml and the mean nasal diameter at nasal valve and middle turbinate level 0.75 ± 0.02 and 0.97 ± 0.02 respectively. Moreover mucociliary transport times were significantly altered in all athletes (mean value ± SD: 19.58 ± 1.92) (18). Nasal resistance and diameters returned within the normal values after the pharmacological nasal decongestion, strongly suggesting the vasomotor nature of the rhinopathy affecting these subjects.

### Rhinitis in boxers

Major rhinosinusal problems experienced by boxers are certainly of traumatic origin. The so called 'boxer's nose' is typically the result of an osteo-cartilaginous nasal fracture with detachment of the distal tip of nasal bones associated with vertical fractures of the cartilaginous septum. These substantial modifications of the nasal anatomy may reasonably lead to significant increase in nasal resistance. In line with this hypothesis, 17 boxers were studied by to Active Anterior Rhinomanometry, Acoustic Rhinometry and mucociliary transport time. As expected, nasal resistance were increased and nasal diameters were significantly reduced in all athletes(18). Moreover, recurrent trauma, often associated with an exasperated use of haemostatic pencils, lead, in boxers, to significant and important alterations at rhinosinusal mucosa level. Specifically the post-traumatic edema, associated with the reflex glandular hyper-secretion, can induce significant alterations of the mucociliary transport system, with the obvious consequence of an increased risk of rhinosinusal infections in these subjects. In a population of boxers, a statistically significant prolongation of mucociliary transport time was found in all subjects (mean value: 27.28 ± 2.21 min) when compared with the general population (18). An increased incidence of anosmia or hyposmia was also observed in these athletes. These data find their rationale in the altered trophism of rhinosinusal mucosa of these subjects, mainly due to the chronic post-traumatic edematous state of the rhinosinusal district. Moreover, repeated traumas can certainly determine a mechanical tearing of olfactory threads.

### Rhinitis in runners

Nasal resistance falls, during exercise, to about half of its resting values. This phenomenon is certainly related to the decongestion of inferior turbinates as a result of the constriction of capacitance vessels. Decongestion begins immediately after starting the physical activity, peaks after about half of an hour of running – for instance – and return to normal values 25–30 min after the end of the exercise. This reduction of nasal resistance is the expression of the increased oxygen, and consequently, blood requirement by the organism during exercise. However, in some predisposed individuals, this chronic alternating variation in nasal resistances values can lead to excessive drying of rhinosinusal mucosa. This dehydration has a double effect: on one hand it determines an alteration of mucociliary transport system for the excessive thickening of secretions, on the other it promotes a rebound increase in nasal secretion (as a physiologic compensatory mechanism of the dehydration itself). The perpetuation of this cycle determine a clinical picture characterized by repeated episodes of watery rhinorrhea and defined as 'runner's nose'. Moreover, the impaired mucociliary transport system predispose to the development of rhinosinusal infections; in addition, this chronic alteration of the trophism of the mucosa can induce recurrent epistaxis. In a recent study of the mucociliary transport time in 30 elite mid-distance runners and in 30 subjects who practiced sports at amateur level, mucociliary transport time, measured immediately after running, was prolonged only in the former (mean value: 20.56 ± 2.35 in elite athletes *vs* 11.93 ± 1.68 in control group), confirming a chronic alteration of rhinosinusal physiology in this kind of athletes (18).

### Recommendations

A comprehensive management plan for athletes with rhinitis should include:

1. Early recognition and diagnosis.
2. Allergy testing.
3. Recognition of associated or subclinical asthma through adequate pulmonary function tests.
4. Avoidance of exposure to relevant allergens (if any) and pollutants during exercise.
5. Treatment to improve nasal symptoms and prevent exercise-induced bronchoconstriction without affecting athletic performance while complying with anti-doping regulations.

## Asthma in athletes

Asthma is defined as a 'chronic inflammatory disease of the respiratory tract in which a number of cells have an important pathogenic role, including mast cells, eosinophils, and T lymphocytes. In susceptible individuals this specific inflammation leads to an increase in airway hyperresponsiveness (AHR) with recurrent episodes of dyspnea, wheezing, coughing, thoracic constriction and shortness of breath that are often reversible either spontaneously or with treatment' (19).

The prevalence of asthma in elite athletes has been reported to range between 3.7% and 22.8% depending on the study population and methods used for diagnosis. Therefore, asthma and asthma-like symptoms seem to be more common in elite athletes compared with age-matched control persons.

Studies performed in comparable population samples also indicate that the disease is on the increase, as its prevalence in US Olympic athletes was 9.7% in 1976 and 16.7% in 1996 (9), and values as high as 21.9% have been reported both at 1998 Nagano Winter Games (20) and at the 2000 Sydney Olympics (8).

Accordingly, the prevalence of bronchial hyperreactivity to metacholine in elite athletes is higher than in controls particularly in swimmers and in athletes exercising in humid environment (21).

Asthma is most commonly found in athletes performing endurance events such as cycling, swimming, or long-distance running(22). Asthma risk is closely associated with atopy and its severity. When the two risk factors, sporting event and atopy, were combined in a logistic regression model, the relative risk of asthma was surprisingly high: 25-fold in an atopic speed and power athlete, 42-fold in an atopic long-distance runner, and even 97-fold in atopic swimmers compared with nonatopic controls (21).

Swimmers (23), ice-hockey players (24) and cross-country skiers (25) have shown a mixed type of eosinophilic, lymphocyte and neutrophilic inflammation in induced sputum samples (23, 24) and bronchial biopsies (25). This inflammation correlates with clinical parameters (i.e. exercise-induced bronchial symptoms and bronchial hyperresponsiveness). It was also shown that mild eosinophilic and lymphocytic airway inflammation was aggravated in swimmers who remained active during a 5-year prospective follow-up study. In contrast, swimmers who stopped active training, eosinophilic airway inflammation, bronchial responsiveness, and clinical asthma attenuated or even disappeared. This prospective study indicated for the first time that intensive training is associated with long-term airway irritation as well as clinical asthma in susceptible individuals, and these changes are at least partly reversible when training is stopped (26).

Similar inflammatory changes have also been reported in endurance athletes who show an increase in airway inflammatory cells associated with changes in exhaled NO after exercise (27).

## The co-existence of asthma and rhinitis

Several epidemiological data indicate that asthma and allergic rhinitis frequently coexist, even in the absence of atopy (28), with rhinitis symptoms being reported in 80–90% of asthma patients, and asthma symptoms reported in 19–38% of patients with allergic rhinitis. A European survey (29) of 1412 subjects with perennial rhinitis and 5198 control subjects found asthma to be present in 16.2% of subjects with rhinitis *vs* 1% of controls. If epidemiological studies indicate that rhinitis and asthma often co-exist (30), prospective studies suggest that rhinitis frequently precedes the development of asthma (31). Moreover, many patients with rhinitis alone demonstrate nonspecific bronchial hyperresponsiveness after exercise or methacholine, this being a risk factor for developing asthma (32).

Severity of allergic rhinitis and asthma has also been shown to be correlated. Patients with allergic rhinitis exhibit eosinophil inflammation in both upper and lower airways (33, 34). In these patients, nasal allergen challenge can induce increased bronchial hyperresponsiveness (35, 36), suggesting that upper and lower airway disorders share common inflammatory features. Proper management of allergic rhinitis also improves asthma control, reinforcing the link between both diseases. In fact, intranasal steroids prevent the seasonal increase in nonspecific bronchial hyperreactivity and asthma symptoms associated with pollen exposure (37). In patients with perennial rhinitis intranasal corticosteroids were also shown to reduce asthma symptoms, exercise-induced bronchospasm, and bronchial responsiveness to methacholine (38, 39). In addition to being safe and effective inhaled corticosteroids are permitted by the WADA and IOC, Medical Commission following notification (40).

Although the pathophysiologic connections between the upper and lower airways are not completely understood, different mechanisms have been proposed, based on both animal and human studies (1).

Certainly, exercise induced asthma (EIA) occurs in a high percentage of patients with allergic rhinitis depending on the type of exercise and outcome measures considered. Moreover, EIA frequently goes undiagnosed in children and athletes (41) because of normal baseline spirometry and negative history of asthma and EIA (42, 43).

### Recommendations

On the basis of all the above, the ARIA recommendation that every rhinitic subject should be screened for asthma should be applied to athletes as well. Standard asthma diagnosis procedures for rhinitic athletes should include spirometry, bronchial challenge with methacholine and field exercise challenge in the relevant sport environment or in the laboratory. For the diagnosis of exercise-induced rhinitis, exercise challenge with specific nasal evaluation (nasal peak flow, functional-rhinomanometry and morphological-acoustic rhinometry) may be specially useful. Ideally, as in other occupational diseases, these tests should be performed before therapeutical interventions.

In major national and international competitions local pollen counts and forecasts (http://www.polleninfo.org;

http://www.aeroallergen.gr) should be made available in advance to allergic athletes, their coaches and medical teams.

## Factors influencing response to exercise

Normal minute ventilation is 7–9 l/min at rest and up to 20–30 l/min during usual activities. It may increase ventilation up to 140–180 l/min for short period of time in speed and power athletes and for longer periods in endurance athletes. Athletes are therefore strongly and repeatedly exposed to large amounts of aeroallergens and pollutants including smoke and chlorine derivatives in swimming. Physical features of the inhaled air also depends on the type of sports and climatic conditions in which exercise is performed, where some athletes are more exposed to others to cold and humid air.

### Allergens

Special attention has been devoted to aerobiological and climatic conditions during special sports event such as Olympics (8).

An aerobiological network was set up for the Athens 2004 Olympic Games to provide information on circulating aeroallergens in three Olympic cities and ensure safety for the allergic athletes who visited Greece from January to September 2004. Records of the most frequently implicated pollen (cypress, hazel, wall pellitory, plane, olive, grasses, goosefoot, mugwort) and fungi spores (*Alternaria* spp., *Cladosporium* spp.) were available. Data were also derived from a 15-year database made in Thessaloniki and Heraklion by the PDUTh. Records from Athens came from the PDUA and concerned a 6-year sampling. Aeroallergen collection was performed by a 7-day recording Burkard volumetric trap in Thessaloniki (1987 until today). Both the above data and the actual aeroallergen daily concentrations were continuously announced by the mass media and Internet beginning 1 year before the holding of the Athens games. Peak pollen concentrations were observed between March and May during the training period for athletes. During the games (August–September) significant concentrations of goosefoot, mugwort, Alternaria and Cladosporium were recorded. Aeroallergens circulated in Athens and Heraklion about 10–20 days earlier than in Thessaloniki. The pollen monitoring adopted for Athens 2004 represents a model of how to help allergic athletes to achieve peak performance under prophylactic measures (http://www.aeroallergen.gr).

### Pollutants

Pollutants have been shown to interact with allergens in inducing sensitization and triggering of symptoms in allergic subjects.

*Sulphur dioxide*. Sulphur dioxide ($SO_2$) and particulate matter (PM) are breakdown products of fossil fuels. They form the most important components of smog ('London-type' smog). Point sources of this form of pollution are power plants although it also occurs from domestic coal burning fires. Levels as low as 20 parts per million (ppm) can be achieved by adopting measures to reduce pollution. Levels as high as 100–500 ppm can occur at times of acute air pollution episodes.

Sulphur dioxide is dissolved in the surface fluid layer of airway epithelium and undergoes a variety of chemical reactions to yield sulphuric acid, sulfites, bisulfites and sulfates. The final common pathway for damage is the release of inflammatory mediators.

Symptoms associated with high levels of $SO_2$ and PM air pollution are wheeze, chest tightness, cough and sputum. They cause bronchoconstriction in subjects with asthma and/or AHR to methacholine (44) and this effect is attenuated by bronchodilators. They can increase morbidity and mortality in patients with underlying chronic bronchitis, asthma and cardiac disease. Studies from Germany showed that $SO_2$ and PM did not increase the prevalence of atopy, hay fever nor asthma in children and adults (28).

*Particulate matter*. Particulate matter of $< 10$ μm (aerodynamically), PM 10, are deposited in the lower respiratory tract. They are associated with both $SO_2$ and ozone pollution. They act by carrying acidic particles into the lower respiratory tract. This gives an increase in respiratory symptom exacerbations and a deterioration in lung function. PM also act by an oxidative effect. These oxidative effects, such as the catalytic actions of transition metals, may alter blood viscosity and increase cardiovascular risks in patients with previous CV disease (45).

*Ozone*. Ozone ($O_3$) is mainly generated from hydrocarbons and $NO_2$ in the presence of ultraviolet radiation (LA smog). Concentrations of 20–40 ppm may occur in the morning, rising to 100 ppm in the afternoon. Ozone may cause respiratory symptoms and increase the annual rate of decline of forced expiratory volume in one second, at levels as low as 80 ppm when exposure occurs over 6 h/day.

Ozone causes transient increases in airway responsiveness. Allergen responses are exaggerated by ozone. This can occur in 1 h in asthmatics exposed to 120 ppm. Nasal allergic responses, in terms of the concentration of eosinophils and eosinophil cationic protein are increased after exposure to ozone.

The cellular and biochemical effects of $O_3$ are to increase neutrophils and prostanoids such as prostaglandins E2 and F2 alpha and thromboxane B2 (46). Treatment or prevention are afforded by bronchodilators, antiinflammatory agents and possibly antioxidants.

*Nitrogen dioxide*. Nitrogen dioxide ($NO_2$) is derived mainly from motor vehicles, power stations and industrial

processes. It also occurs in the work place and can contribute to indoor air pollution. $NO_2$ is associated with frequency and duration of respiratory illness and functional impairment in children. Most studies in adults are confounded by the strong associations between different air pollutants.

Normal subjects are little affected by exposure to $NO_2$. In asthmatics this enhances airway responsiveness to methacholine and bronchoconstriction induced by exercise (EIB) or cold air hyperventilation (47).

Brochoalveolar lavage (BAL) studies in healthy subjects shows a reduction in alpha 1 proteinase inhibitor. Mast cells and neutrophils are increased in BAL.

Antihistamines and antioxidants protect against the effects of $NO_2$.

*Smoke*. Smoke is one of the recognized factors influencing both the onset of acute respiratory symptoms and the progression of chronic bronchial inflammation.

Approximately 12 000 compounds have been isolated in the tar, the product of tobacco combustion, and more than 4500 components have been identified. The main compounds are: carbon dioxide, carbon monoxide, cianidric acid, nitrous acid, aldehydes, phenols, alkaloids (such as nicotine), arsenic, radioactive elements and polycyclic aromatic hydrocarbons. These compounds are also present in the exhaled air and in the surrounding air at the moment in which the smoker is not inhaling from the cigarette, and tar is deposited when smoke is cooled or dissolved so that their concentration in the environment can be up to four times of those present in the inhaled smoke. Therefore both active and passive smoking are involved in the generation of respiratory diseases.

Active smoking is related to the severity of asthma and to the reduced response to pharmacological treatment. Also at least the 10% of smokers' blood is bound to carbon monoxide, which reduces the muscular efficiency and induces a further hyperventilation, thus increasing the possibility of exercise induced asthma and enhancing the allergens inhalation. Smokers were also shown to have increased IgE levels independently of the presence of sensitization to common allergens (48), which is suggestive of the possibility that smoke promotes a Th2 response. Moreover smoke is able to activate the expression of the genes involved in mucus secretion, this promoting both bronchial obstruction and tissue remodeling (49).

Epidemiological studies have suggested that 'second hand smoke', also know as Environmental Tobacco Smoke (ETS) increases the incidence and the severity of allergies and asthma. Recently it was demonstrated that ETS up-regulates the allergic response to inhaled allergens, acting as an adjuvant for Th2 responses, specifically increasing IL-4 and IL-10 (50). Intense exercise can rise the quantity of inhaled air from 5 up to 120 l/m, this make the composition of air present in the environment crucial for the induction of respiratory symptoms.

Taken together these considerations indicate important interactions among allergy, exercise and smoke and these should be seriously considered in organizing physical activity at any level, from elite athletes to amateurs and at any ages, with a particular attention to school and sports environments, and student's behavior, as reported more and more frequently in teenagers school teams (51–53).

However, at present there are no epidemiological data on smoking habits in professional or amateurs athletes.

This gap should be filled starting from epidemiology and the first possibility is to include in any survey concerning physical exercise specific questions about smoke habits and quality of the environment.

## Diagnosis of asthma in athletes

Because some anti-asthmatic drugs are banned by the current anti-doping regulations (40), methods for diagnosis of asthma in athletes must be accurate and standardized, but should also ensure that criteria requested should not come in conflict with an optimal treatment of the disease as codified by the current international guidelines (19).

The sensitivity and specificity of parameters used for diagnosis of asthma in athletes largely depends on the threshold chosen as limit of normality. Accordingly, a distinction should be made between asthmatic athletes or athletes with a history of asthma and apparently healthy athletes or rhinitic athletes (who should always be studied for asthma).

### Subjective and objective symptoms

Standardized questionnaire should be used for recording of symptoms suggestive of airways obstruction at rest or in relation to exercise, at night or during pollen season as well as of previous treatments.

### Spirometry

Pulmonary function tests may be normal in athletes whether predicted values are referred to the normal sex- and age-matched population.

### Provocation tests

Both indirect (eucapnic voluntary hyperventilation [EVH], exercise) and indirect (methacholine) may be used to reveal bronchial hyperreactivity. Indirect tests are more specific but less sensitive whereas direct tests are sensitive but have low specificity.

*Reversibility after administration of a permitted β-agonist*. A 12% or greater increase of the predicted value of forced expiratory volume in 1 s ($FEV_1$) is at present considered by IOC regulations as a sign of reversible airways

obstruction. This criterion, proposed by ERS, differs from the ATS criteria according to which a positive response is defined as a 12% increase from basal value and at least 200 ml. For instance, an athlete with a basal $FEV_1$ of 4.50 l and a predicted value of 5.00 l (83% of predicted) with an increase after a permitted inhaled beta-agonist of 0.54 l (12% of basal value) would be defined as irreversible by ERS and reversible by ATS. Moreover, athletes have $FEV_1$ higher than predicted, which makes rare a 12% or greater increase from basal values even in the presence of mild asthma.

*Eucapnic Voluntary Hyperventilation test*. A 10% or greater decrease in Single stage or Multistage EVH test has been suggested to document hyperreactive airways in athletes.

*Exercise tests*. Athletes and amateur exercisers with reactive airways disease may experience bronchoconstriction following, or even during, exercise, which may hamper successful completion a given exercise task (54). Exercise-induced bronchoconstriction has been reported up to 80% of the population with clinically recognized asthma. Therefore, exercise is used as a challenge test to detect EIB in asthmatic patients, with, or without, respiratory symptoms during or after exertion. EIB cannot be excluded by a negative methacholine test (55). Moreover, many children and adults with documented EIB, have no symptoms of asthma. Recently a 30% incidence of EIB in a large group of elite athletes has been reported, while respiratory symptoms were only present in 5% of subjects (56). In a cold environment the incidence of EIB, in subjects without clinical diagnosis of asthma, may be even higher (57). An exercise challenge is therefore often worthwhile for subjects in which exercise could be limited by EIB. Preferably, the type of exercise should be chosen to be consistent with the type of sport practised.

Respiratory water loss and/or cooling has been invoked as the potential causes of airways narrowing; at present, there is no direct experimental evidence to support either of these hypothesis. However, these proposals led to the conclusion that exercise protocols for the detection of EIB should aim to achieve high levels of ventilation (V'E 15–22 times greater than resting forced expiratory volume at first second, $FEV_1$) while breathing air containing $< 10$ mg/l of water (20–25°C and $< 50\%$ relative humidity) (58, 59). Breathing compressed air *via* a Douglas bag, tubing and valve will ensure the low humidity of inspired air. The required V'E can be achieved by either running on a treadmill or by cycling. Exercise on a cycle ergometer is usually preferred because work rate can be measured accurately. If V'E is not measured, target work rate can be estimated by equations relating V'E to oxygen uptake ($\dot{V}O_2$) and $\dot{V}O_2$ to work rate [e.g. watts = (53.76 measured $FEV_1$) – 11.07] (58, 59). Alternatively, 90–95% of predicted maximal heart rate (pred. $HR_{max}$ = 220-age years) can be used to monitor exercise intensity (55, 58, 59).

The exercise protocol recommended consists in a rapid (3–4 min) increase in work rate to the target value that should be maintained for 4–6 min (55, 58, 59); for the 1st, 2nd and 3rd min of running (preferably) or cycling work rate may be conveniently set to 60%, 75% and 90% of the target value. $FEV_1$ should be measured at rest and in the first 20 min of recovery; a fall of $> 15\%$ (*vs* baseline value) is regarded as diagnostic of EIB (34, 35). In subject with EIB, $FEV_1$ generally falls to reach a minimum within the first 10 min after cessation of exercise, with substantial recovery by 30-min postexercise. Airway cooling and drying, induced by exercise, are also thought to stimulate the release of inflammatory mediators, such histamine and leukotrienes (60). Thus, exercise has become an important challenge method for assessing the effects of asthma medications. A drug to be 'protective' should reduce the maximal decrease of $FEV_1$ after exercise by $> 50\%$ (58, 59). To maximize the likelihood of a positive response, bronchodilator agents should be withheld prior to exercise for a period commensurate to their duration of action (58, 59).

Some recommendations should be followed for exercise testing (Table 1):

*Methacoline challenge*. The methacoline challenge when performed with the available standard procedure is to be the most widely used and accurate test to prove airways hyperreactivity (55).

The thresholds indicated by the IOC (IOC rules have been recently changed for Turin 2006 [http://www.olympic.org]) – a PD20 $< 1$ μmol (200 μg) or a PC20 $< 2$ mg/ml and a PD20 $< 6.6$ μmol (1320 μg) or a PC20 $< 13.2$ mg/ml for athletes on topical steroids – seem however to be adequate to identify moderate and severe asthmatic but might fail to identify mild or subclinical asthma or asthma under control with treatment. In fact, the sensitivity of methacoline challenge for confirming or rejecting the diagnosis of asthma is greatly dependent on the pretest probability of asthma and the PC20.

## Management

### Immunotherapy

Allergen immunotherapy is a biological response modifier. It alters the immune response to allergens at early stages, thus resulting in diminished symptoms and need for drugs. Its efficacy has been proven for both rhinitis and asthma, and the association of the two diseases is the optimal indication (61). IT must be prescribed and administered only by trained physicians, after a careful diagnostic and cost/benefit evaluation. There is no contraindication to immunotherapy in athletes and those practicing sports. The only precaution should be to avoid physical exercise just after receiving the injection. The

Table 1. Recommendations for exercise testing

- For safety reasons in adults, $FEV_1$ at rest should be >75% predicted or >80% of the subject best value (if known)
- Medications should be withheld: 6 h for short-acting bronchodilators and sodium cromoglycate; 12 h for long-acting bronchodilators, theophylline, and antihistamine; no steroid or caffeine in the study day
- Breathing compressed air at controlled temperature to better standardize the test (compressed air usually cools inhaled air) is recommended. Room air containing <10 mg/l
- $L^{-1}$ of water (i.e. <25°C and <50% of relative humidity) is considered adequate. Cold air is needed only if it represents environmental conditions (e.g. country skiers, ice skating)
- $FEV_1$ measurement is mandatory, pre-exercise and 1, 3, 5, 7, 10, 15 and 20 min postexercise
- Constant work-rate exercise (cycle ergometer or treadmill at specific exercise depending on the discipline practised); exercise intensity should elicit 40–60% of predicted maximum voluntary ventilation ($MVV = FEV_1 \times 40$) and maintained for 4–6 min. Target work rate can be estimated by equations relating V'E to oxygen uptake ($V'_{O_2}$) and $V'_{O_2}$ to work rate [e.g. watts = (53.76 measured $FEV_1$) − 11.07]. Alternatively, 90–95% of predicted maximal heart rate (pred. $HR_{max}$ = 220-age years) can be used
- A fall in $FEV_1$ of >10% is considered abnormal, while a fall of 15% is regarded as diagnostic of EIB
- If patients are not taken inhaled or oral steroid, a fall in FEV1 of >10 <25% is considered mild; >25 <50% is considered moderate, >50% is considered severe
- Rapid acting bronchodilator (e.g. salbutamol) should be available to reverse severe bronchospasm

recent introduction of sublingual immunotherapy has greatly increased the safety of this treatment (62).

### Antihistamines

Oral H1 antihistamines are one of the first-line therapeutic options for allergic rhinitis (1). However, they might affect vigilance and reaction time in athletes. The new generation molecules have high selectivity, long half lives and also possess antiallergic activities (63). In athletes, the main concern with antihistamines is the possible sedative effect (64). Although this side-effect is at least in part variable from an individual to another, the newest molecules (cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, ebastine, mizolastine) proved to be devoid of sedative effect at the usual therapeutic doses. Molecules not undergoing liver metabolism (cetirizine, desloratadine, fexofenadine) have the additional advantage of avoiding possible drug-to-drug interactions and rare but severe cardiotoxic effects (65, 66).

### Antileukotrienes

The available leukotriene receptor antagonists (zafirlukast and montelukast) are now widely accepted as part of the general therapeutic plan for asthma treatment (19). In elite athletes and amatorial exercisers antileukotrienes proved highly effective in protecting against exercise-induced bronchospasm, and can therefore be given in substitution of the β2-agonist premedication. However, in a controlled study montelukast did not ameliorate asthma-like symptoms in ice hockey players (68). No particular contraindication for antileukotrienes in those practicing sports has so far emerged for antileukotrienes (67) which are included among drugs permitted by IOC for asthmatic athletes with no limitations.

### Topical steroids

Highly effective as controller drugs for asthma, their use in athletes has requested notification and a physician's declaration from 1993 to 2002. At present no regulation is set by the IOC upon the use of topical steroids in athletes although regulations differ among various international sports associations and some of them still follow previous requirements. A therapeutic use exemption form is requested by WADA for all topical steroids except dermatological formulation (40).

### Inhaled beta-agonists and anti-cholinergics

From the early 1990s there has been a marked concern regarding the use of asthma drugs among elite competitive athletes, especially in endurance sports. In 1993 the IOC Medical Commission decided that only the two short-acting inhaled β2-agonists, salbutamol and terbutaline, were allowed for the use in competitive sports. The use should have been declared and accompanied by a physician's declaration. The same regulations were made for inhaled steroids. Concern was made due to the reports that β2-agonists systemically given in large doses might influence skeletal and heart ventricular musclefibers in research animals. However, there is no solid evidence that short acting inhaled β2-agonists do improve performance in athletes. This uncertainty also extends to the long acting β2-agonist salmeterol, which has been allowed since February 1, 1996, and formoterol which has been allowed since September 1, 2002. At this time the World Anti Doping Agency (WADA) had been established, and the doping regulations became the joint regulations given by WADA and the IOC Medical Commission. From this date the regulation for asthma drugs only concerned the β2-agonists, as no regulations were given regarding inhaled steroids. However, some confusion exists, as regulations differ somewhat between the different International sport Associations. Confusion was also evident for the Winter Olympic Games in January 2002. The IOC Medical Commission sent out preliminary regulations for these games, only weeks before the Games, including required limits for metacholine provocation (PD20, PC20), levels for responses to bronchodilators and for exercise

Table 2. Permitted and prohibited anti-allergic treatments

| Treatment | WADA rules | Notes |
|---|---|---|
| Antihistamines | Permitted | Second generation antihistamines should be preferred to avoid cardiotoxic effects and somnolence |
| Antileukotrienes | Permitted | |
| Oral steroids | Prohibited in competition, require Therapeutic Use Exemption approval | |
| Topical steroids | Require an Abbreviated Therapeutic Use Exemption | Topical preparations for dermatological aural/otic, nasal, buccal cavity use are not prohibited |
| Oral beta-2 agonists | Prohibited | |
| Inhaled salbutamol, terbutaline, formoterol, salmeterol | Require an Abbreviated Therapeutic Use Exemption | A concentration of salbutamol >1000 ng/ml is considered an Adverse Analytical Finding unless proven as due to therapeutic use of inhaled salbutamol. The IOC (http://www.olympic.org) has set criteria for diagnosis of asthma |
| Ephedrine, methylephedrine | Prohibited in competition Pseudoephedrine permitted | Ephedrine and methylephedrine concentration in urine >10 μg/ml represent Adverse Analytical Findings |
| Immunotherapy | Permitted | Subcutaneous immunotherapy injections should not be performed before or after physical exercise |

The World Anti-doping Agency (WADA) Code. The 2006 Prohibited List, effective January 1, 2006 (http://www.wada-ama.org).

testing. As treatment of asthma has a long term perspective, it may be stated that this initiative was in conflict with the common guidelines for asthma treatment (69).

Presently, the latest WADA regulations do not employ predefined limits of bronchial hyper responsiveness or EIB, but requires an extensive documentation (70).

Due to the extensive use of asthma drugs among top endurance athletes, documentation is clearly required. However, as the present rules and definitions may be confusing, there is clearly a need for defining diagnostic criteria for exercise induced asthma and bronchial hyper responsiveness in athletes, work out guidelines for the treatment and refine the present doping regulation. The doping regulations should also be harmonized among the different sport associations. Certainly, for asthmatic athletes should be reserved the same management plan (topical steroids, antileukotrines, combination therapy) recommended by asthma guidelines to all asthmatic subjects (http://www.ginasthma.com). Anticholinergic drugs (ipratropium bromide, etc.) may be beneficial before exercise in rhinitic athletes, particularly in vasomotor and cold rhinitis (71).

### Oral, intravenous or intramuscular drugs

Oral, intravenous, or intramuscular steroids and beta-agonists are not permitted in athletes by IOC-WADA regulations (Table 2).

It seems that athlete asthma is difficult to treat. Inhaled corticosteroids are only partly effective, probably because the inflammation has an irritant feature demonstrated by an increased proportion of neutrophils as well as eosinophils in induced sputum samples. In symptomatic ice-hockey players, a recent study showed that even montelukast was ineffective. Bronchodilators offer only limited relief because well performing athletes do not usually show significant bronchoconstriction even though they may suffer from intensive cough and sputum production.

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