

# Exercise and Airway Injury in Athletes



## Exercício e Dano das Vias Aéreas em Atletas

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*Acta Med Port* 2013 Jan-Feb;26(1):56-60

### ABSTRACT

Olympic level athletes present an increased risk for asthma and allergy, especially those who take part in endurance sports, such as swimming or running, and in winter sports. Classical postulated mechanisms behind EIA include the osmotic, or airway-drying, hypothesis. Hyperventilation leads to evaporation of water and the airway surface liquid becomes hyperosmolar, providing a stimulus for water to move from any cell nearby, which results in the shrinkage of cells and the consequent release of inflammatory mediators that cause airway smooth muscle contraction. But the exercise-induced asthma/bronchoconstriction explanatory model in athletes probably comprises the interaction between environmental training factors, including allergens and ambient conditions such as temperature, humidity and air quality; and athlete's personal risk factors, such as genetic and neuroimmuneendocrine determinants.

After the stress of training and competitions athletes experience higher rate of upper respiratory tract infections (URTI), compared with lesser active individuals. Increasing physical activity in non-athletes is associated with a decreased risk of URTI. Heavy exercise induces marked immunodepression which is multifactorial in origin. Prolonged, high intensity exercise temporarily impairs the immune competence while moderate activity may enhance immune function. The relationship between URTI and exercise is affected by poorly known individual determinants such genetic susceptibility, neurogenic mediated immune inflammation and epithelial barrier dysfunction. Further studies should better define the aetiologic factors and mechanisms involved in the development of asthma in athletes, and propose relevant preventive and therapeutic measures.

**Keywords:** Asthma, Exercise-Induced; Bronchial Hyperreactivity; Exercise; Sports.

### RESUMO

Os atletas olímpicos têm um risco aumentado de asma e alergia, principalmente aqueles que participam em desportos de resistência, tais como natação ou corrida, e em desportos de inverno. Os mecanismos clássicos subjacentes à asma induzida pelo exercício (AIE) incluem a hipótese osmótica, por desidratação das vias aéreas. Devido à hiperventilação, a evaporação da água da superfície das vias aéreas estimula o movimento da água a partir das células vizinhas, resultando em contração celular e libertação de mediadores inflamatórios que causam a contração do músculo liso. Mas o modelo explicativo de AIE/broncoconstrição em atletas provavelmente inclui a interação entre fatores ambientais, incluindo fatores relacionados com o treino, alérgenos e condições ambientais, tais como temperatura, humidade e qualidade do ar, bem como fatores de risco pessoais do atleta, como determinantes genéticos e neuro-imuno-endócrinos.

Os atletas, comparativamente a indivíduos menos ativos, têm maior taxa de infeções das vias aéreas superiores (IVAS) após o stress do treino e competições. O aumento da atividade física em indivíduos não-atletas associa-se a uma diminuição do risco de IVAS. O exercício intenso induz imunodepressão marcada, de origem multifatorial. A atividade física moderada pode melhorar a função imunológica, enquanto o exercício de alta intensidade, prolongado, prejudica temporariamente a capacidade imunológica. A relação entre exercício e IVAS é afetada fatores pouco conhecidos, incluindo determinantes individuais de suscetibilidade genética, inflamação neurogénica imunologicamente-mediada e disfunção da barreira epitelial. Os fatores etiológicos e mecanismos envolvidos na asma em atletas deverão ser alvo de estudos futuros no sentido de permitir propor medidas pertinentes de prevenção e terapêutica.

**Palavras-chave:** Asma Induzida pelo Exercício; Exercício; Desporto; Hiperreactividade Brônquica.

### INTRODUCTION

In 2008, a jointed initiative endorsed by the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology, defined exercise-induced asthma (EIA) as lower airway obstruction and symptoms of cough, wheezing or dyspnea induced by exercise in patients with underlying asthma.<sup>1</sup> The reduction in lung function (forced expiratory volume in 1 s (FEV1)) occurring after a standardized exercise test is called exercise-induced bronchoconstriction (EIB). These definitions are however limited by the heterogeneity in asthma expression. In fact, multiple asthma phenotypes exhibiting differences in the clinical response to treatment exist.<sup>2</sup> Therefore, assessment should be multidimensional, including variabil-

ity in clinical, physiologic, and pathologic parameters. Two different clinical phenotypes of asthma in athletes, reflecting different underlying mechanisms, have been recently suggested by Haahtela, et al.<sup>2</sup> The pattern of *classical asthma* characterized by early onset of asthma in childhood, bronchial hyperresponsiveness diagnosed by methacholine challenge, atopy and signs of eosinophilic airway inflammation; and another distinct phenotype with onset of symptoms during sports career, bronchial responsiveness to eucapnic hyperventilation test and a variable association with atopic markers and eosinophilic airway inflammation.

Despite extensive investigation, the prevalence of EIA/EIB in athletes remains surrounded by some discrepan-

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Recebido: 10 de Setembro de 2012 - Aceite: 22 de Dezembro de 2012 | Copyright © Ordem dos Médicos 2013

cies in the literature. Differences between studies in what concerns to definition, diagnostic methods and techniques, population, gender and age, country, season, environment, and sports type contribute for the observed divergence.<sup>3,4</sup> It has generally been recognized that it is more frequent than in general population, as well as more prevalent in elite athletes (particularly those who participate in endurance events such as cross-country skiing, swimming, road cycling and long-distance running) than in recreational athletes.<sup>1,3,5</sup> Its prevalence in winter sports, swimming, and endurance disciplines has been reported to reach values up to 54,8%.<sup>6,7</sup> Moreover, it has been identified that the risk of asthma is 25-fold higher in atopic speed and power athletes, 42-fold greater in atopic long-distance runners, and 97-fold higher in atopic swimmers compared with healthy nonatopic control subjects<sup>1</sup>. Asthma is definitely the most common chronic medical condition among Olympic athletes,<sup>8</sup> with obvious implications for their health and quality of life.

Classical postulated mechanisms behind EIA include the osmotic, or airway-drying, hypothesis.<sup>9</sup> Hyperventilation leads to evaporation of water and the airway surface liquid becomes hyperosmolar, providing a stimulus for water to move from any cell nearby, which results in the shrinkage of cells and the consequent release of inflammatory mediators that cause airway smooth muscle contraction. However, as this stimulus is present in all athletes, it would be expectable that all end up developing bronchoconstriction. That, however, does not occur, which led to speculate a more comprehensive explanatory model of EIA/EIB in athletes, in which the interplay between environmental training factors (including allergens and ambient conditions - e.g. temperature, humidity and air quality) and athlete's personal risk factors, such as genetic and neuroimmunoendocrine determinants, probably plays a key role.

Although the pathogenesis is not fully elucidated, some other hypotheses have been proposed to explain how vigorous and repeated physical activity may cause EIA/EIB in athletes. Disruption to the airway epithelium has been pointed out as implicated in this process, as previous findings have suggested that the airway epithelium of athletes may be injured by strenuous exercise.<sup>10,11</sup> Also, an increase in the levels of airway vascular permeability have been shown to predict the severity of EIB in asthmatics,<sup>12</sup> which has led to the microvascular theory of EIB based on functional abnormalities of endothelial cells in newly generated microvessels in asthmatic airways.<sup>13</sup>

Other explanatory hypothesis focuses upon cooling of the airways caused by increased ventilation. Vigorous exercise requires an increased ventilatory rate to meet higher muscular oxygen needs, which results in the inhalation of a large volume of relatively cold and dry air and the loss of heat, besides water, from the respiratory mucosa. This mechanic noxious stimulus, together with the abovementioned osmotic mechanism, could cause epithelial damage, and therefore the influx of inflammatory cells and their mediators' release.<sup>1,3</sup>

Moreover, cooling of the airways also causes reflex

parasympathetic nerve stimulation; this leads to bronchoconstriction through stimulation of the vagal nerve, initially causing reflex vasoconstriction of bronchial venules to conserve heat, followed at the end of the exercise by secondary reactive hyperemia (airway rewarming) with vascular bronchial congestion, edema, and further airway narrowing.<sup>14</sup> It has been hypothesized that repeated intensive training could provoke vagal hegemony, responsible for the well-known resting bradycardia of athletes, but possibly also predisposing to an increase in the bronchomotor tone with consequent increased susceptibility to bronchospasm.<sup>15</sup> This hypothesis of a generalized dysautonomy associated with training has been supported by an increasing body of evidence. A few years ago, a correlation was observed between vagal activity and maximal oxygen uptake ( $\text{VO}_{2\text{max}}$ ).<sup>16</sup> Later, autonomic nervous system activity in athletes assessed by pupillometry showed an increased parasympathetic activity and a reduced sympathetic activity in the pupillary light reflex.<sup>17</sup> More recently, Pichon, et al.<sup>18</sup> found that subjects with an increased bronchial hyperresponsiveness had a higher vagal tone, corroborated by Park, et al.<sup>19</sup> findings of a relationship between methacholine bronchial responsiveness and diminished sweat secretion, tearing and salivary flow rate in healthy athletes.

This dysfunctional neuro-immune interface may play a role in the pathogenesis of EIB, mainly due to release from primary sensory nerve terminals of neuropeptides, in a so called *neurogenic inflammation* pathway. This hypothesis is corroborated by the findings of increased circulating levels of substance P, one of the *major* initiators of neurogenic inflammation, after strenuous exercise.<sup>20</sup> Transient receptor potential vanilloid 1 (TRPV1) is the centre of almost all neuronal inflammatory signaling pathways, as this ion-channel is often co-localized with sensory neuropeptides in the same axon of a primary neuron, and its stimulation can lead to release of these substances. It is expressed in primary sensory neurons, pulmonary smooth muscle cells, bronchial and tracheal epithelial cells and dendritic cells in the lung.<sup>21</sup> Known physical activators of these channels include noxious temperature (heat or cold), changes in membrane potential, mechanical or osmotic stress, and arachidonic acid metabolites.<sup>22</sup> Associations between the levels of cysteinyl leukotrienes (cysLTs) and of neuropeptide neurokinin-A in the airways have been found in patients with EIB, underlying the association between these events; the mechanism is probably related to cysLT-mediated activation of sensory airway nerves.<sup>23</sup>

Furthermore, an additional detrimental effect to the airways in some specific sports, probably comes from environmental training and competing conditions. For instance, the cold and dry air in athletes practicing winter sports, the ultra-fine airborne particles emitted from ice resurfacing machines in indoor ice rinks,<sup>24</sup> the pollen and pollutants exposure in athletes practicing outdoor,<sup>25</sup> as well as the chemical exposure to a chlorine-rich atmosphere and microaspiration of water droplets for swimmers<sup>2</sup>. The *'pool chlorine hypothesis'* followed the observation that an increased risk of de-

veloping asthma occurred among young children regularly attending a pool, hypothesizing that childhood asthma rise in industrialized countries could be related to their exposure to chlorination by-products contaminating the air of indoor swimming pools.<sup>26</sup>

In fact, in swimming Belgian schoolchildren a relation was established, in a dose dependent manner, between attending pool and the prevalence of asthma, exercise-induced bronchoconstriction and markers of epithelium damage in the lungs.<sup>27</sup> These data led to speculate whether an airway epithelium barrier dysfunction could predispose to easier penetration of aeroallergens and therefore be responsible for higher rates of sensitization and atopic diseases. However, the analysis was carried out as if there were independent observations of asthma and swimming pool use, while there was *clustering* of asthma by school, even after allowing for effects of swimming pool use and other covariates.<sup>28</sup> Later, in the International Study of Asthma and Allergies in Childhood (ISAAC) a relation was observed between prevalence of wheeze, asthma, hay fever, rhinitis and atopic eczema and the number of indoor chlorination swimming pools in the European centers involved in the study.<sup>29</sup> Nevertheless, information retrospectively collected from 2606 adults, showed no association between asthma and swimming pool attendance, although those frequently exposed at school age presented higher rates of hay fever.<sup>30</sup> Although epidemiological cross sectional data seems to support a role for chlorine exposure in asthma incidence, until now in only three specific situations a confirmation of an occupational risk with development of a specific swimming pool-induced asthma was possible.<sup>31</sup>

In the specific case of competitive athletes, the evaluation of airway damage poses several issues unique to this population. The first issue regards symptoms, as they have been shown to be poor predictors of asthma in athletes.<sup>32-34</sup> The heavy training, with the extremely high level of physical fitness and  $VO_{2max}$  reached, turns difficult to discriminate between physiological and pathological limitations to maximum exercise.<sup>3</sup> On the other hand, some athletes fear that admitting to have asthma will be detrimental and so do not reveal their symptoms, while others without asthma will try to gain a competitive advantage by asthma treatments<sup>35</sup> (although several studies have proved that anti-asthmatic drugs do not enhance performance in healthy subjects,<sup>36-38</sup> this is still a general misbelieve). Therefore, objective evidence of airway damage and asthma is recommended in these subjects.<sup>39</sup>

Asthma assessment should be multidimensional and due to the above mentioned facts, requires either a positive bronchodilator or bronchoprovocation test to validate diagnosis,<sup>39,40</sup> as baseline spirometry is poorly predictive of asthma in competitive athletes. They often record lung function values higher than the general population; they may appear to be within the *normal* range, although, in reality, show a pulmonary deficit on the basis of what is expected for an athlete.<sup>1,41</sup> A special consideration should be made addressing cases of athletes with known asthma who seek approv-

al for the use of a inhaled  $\beta_2$ -agonist, but due to a well-controlled status record a negative result in the bronchial provocation tests (it should be remembered that according to 2012 WADA guidelines, all  $\beta_2$ -agonists are prohibited except salbutamol, formoterol and salmeterol when taken by inhalation).<sup>42</sup> In these cases, the negative result should be not be interpreted as a misdiagnosis but as improvement in relation to a well-designed therapeutic strategy. The following data must be taken into account: appointments with their physician, hospital emergency department visits or admissions for acute asthma exacerbations or oral corticosteroids treatment, asthma's onset age, detailed description of both day and night symptoms, triggering factors and medication, past or current atopic disorders together with skin prick tests or specific IgE results, and physical examination.

### Respiratory tract infections in athletes

During periods of heavy exercise and for a couple of weeks following competition events athletes may be at increased risk of upper respiratory tract infection related to practicing regular strenuous exercise.<sup>43,44</sup> Prolonged and intensive exertion, in contrast to moderate or intermittent physical activity, cause changes in immunity that are possibly consequence of physiological stress and suppression. It has been suggested that the relationship between URTI and exercise follows a "J-curve", with moderate and regular exercise improving the ability to resist infections,<sup>45-47</sup> while heavy acute or chronic exercise decreasing it.<sup>48-50</sup>

Many studies addressed explanations on how the susceptibility to URTI may be increased by acute and exhaustive exercise (for a review see Gleeson).<sup>51</sup> Intense exercise is known to decrease the expression of Toll-like receptors and to increase IL-6, epinephrine and cortisol production, leading to an impaired cell-mediated immunity and low-grade inflammation, via a decreased cytokine production from macrophages and Th-1 cells.<sup>51</sup>

Evidence arising from epidemiologic reports suggests an increased risk of URTI among athletes engaging in strenuous exercise, such as heavy training or a marathon. The odds for a self-reported URTI observed in study including 2311 marathon runners (who varied widely in running ability and training habits) was six fold higher in those participating in the 1987 Los Angeles Marathon compared with those who trained but missed the race.<sup>50</sup> Subsequent studies from Peters et al. have partially supported this observation.<sup>52,53</sup> In a double-blind placebo controlled trial, assessing the effects of antioxidants supplementation, symptoms of URTI after the race were more common in the placebo group than in the sedentary controls.<sup>53</sup> In other study, the incidence of self-reported URTI symptoms was higher in runners who trained hardest.<sup>52</sup>

However, these findings are not homogenous. In another study by Nieman et al,<sup>54</sup> in marathon runners no increased prevalence of URTI was observed during the week after 5-km, 10-km, and 21.1-km events as compared with the week before. Runners who trained more than 25 km per week had lower rate of infections, although non-signif-

icant.<sup>54</sup> These findings suggest either no change, or even a slight reduction, in the risk of sickness during the week after a run. A similar observation was reported in a study by Heath et al.<sup>55</sup> where the odds ratio for URTI increased with averaged running distance until 1388 miles per year, but decreased thereafter. In a longitudinal observational study including long-distance runners with serial monitoring of training loads and clinical patterns of illness no effect was found of training mileage, intensity, and load on the incidence of respiratory illness.<sup>56</sup> The most challenging observation comes from the Ekblom et al trial.<sup>57</sup> In a representative sample of runners of the Stockholm Marathon, no increase in URTI was observed in healthy subjects after the race. That is, the post-race infection episode incidence, if runners with at least one self-reported pre-race infection episode are excluded from the analysis, is equal to the self-reported incidence before the marathon. Neither running time nor pre-race training volume, nor gender or social status could explain the incidence of post-race infec-

tion episode. However, faster finishing time, especially in younger runners, in relation to pre-race training status, may be a risk factor. These data supported an extension of the "J" to an "S" curve, emphasizing the need in the elite athlete of an immune system able to withstand infections during severe physiological and psychological stress besides an extremely prepared physique system.<sup>58</sup>

In conclusion, studies looking at the impact of physical activity or exercise on infection's susceptibility varied widely in respect to exercise load, subjects, and methods. Although the hypothesis relating the risk of disease with amount of exercise, the "J" shaped curve, has been accepted by athletes, coaches and scientists, there is currently no sufficient evidence to support it. However, there appears to be an association between strenuous effort, such as marathon running, and increased susceptibility to infection. Individual factors certainly play an important role. In high fit subjects, such as Olympic level athletes, the association between exercise load and risk of URTI may tend to flatten.<sup>59</sup>

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