Exercise-induced asthma: why is it so frequent in Olympic athletes?

Expert Rev. Resp. Med. 5(1), 1–3 (2011)

André Moreira

Author for correspondence: Department of Immunology, Faculty of Medicine, University of Porto, Al. Prof. Hernâni Monteiro, 4200 Porto, Portugal and Immunoallergology, Hospital São João, Porto, Portugal andremoreira@med.up.pt

Luís Delgado

Department of Immunology, Faculty of Medicine, University of Porto, Porto, Portugal and Immunoallergology, Hospital São João, Porto, Portugal

Kai-Håkon Carlsen

Oslo University Hospital, Rikshospitalet, Department of Paediatrics, Oslo, Norway and Norwegian School of Sport Sciences, Oslo, Norway

"A consistent body of evidence has shown that Olympic-level athletes have an increased risk for asthma and allergy, especially those who take part in endurance sports, such as swimming or running, and in winter sports."

In 2008, the PRACTALL 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 [1]. The same clinical presentation in individuals without asthma was defined as exercise-induced bronchoconstriction (EIB). However, these definitions are limited by the heterogeneity in asthma expression. In fact, multiple asthma phenotypes exhibiting differences in clinical response to treatment exist and assessment should be multidimensional, including variability 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.*: the pattern of 'classical' asthma, characterized by early onset childhood asthma, methacholine responsiveness, 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 [2].

A consistent body of evidence has shown that Olympic-level athletes have an increased risk for asthma and allergy, especially those who take part in endurance sports, such as swimming or running, and in winter sports [3]. Data from the first pan-European study on allergy and asthma in Olympic athletes – the GA2LEN Olympic study – revealed that one in four of the European athletes participating in the Beijing Olympic Games reported chest tightness and wheeze and one out of three reported exercise-induced shortness of breath [GA2LEN Olympic Study Coordinating Centre, Oslo, Norway, Data on File]. Classical postulated mechanisms behind EIA include the osmotic, or airway-drying, hypothesis [4]. As water is evaporated from the airway surface liquid, it becomes hyperosmolar and provides an osmotic stimulus for water to move from any cell nearby, resulting in cell shrinkage and release of inflammatory mediators that cause airway smooth muscle contraction. However, a proof of concept of this hypothesis would require that all athletes would develop bronchoconstriction at a certain point. This does not happen, suggesting the EIB explanatory model in athletes will probably include the interplay between environmental training factors, including allergens and ambient conditions such as temperature, humidity and air quality, and an athlete's personal risk factors such as genetic and neuroimmunoendocrine determinants.

Genetic susceptibility to EIB has been linked with the gene for the aqueous water channel aquaporin 5. Airway hydration during exercise is mainly dependent on the water movement, following the osmotic force generated by sodium and chloride, through aquaporin channels expressed

Keywords: asthma • athletes • Olympic

 10.1586/ERS.10.88 ISSN 1747-6348

within the apical membrane of epithelial cells. It has been suggested that functional polymorphisms of aquaporin 5 may contribute to a phenotype where hyperhidrosis, sialorrhea and excessive tearing are traits that may predict resistance of airways to nonspecific stimulus [5]. However, it is also possible that mechanisms affecting both water and ion movement are commonly affected by nervous system dysfunction.

Intensive training can have effects on autonomic regulation and cardiac function, promoting the vagal predominance, thus regulating contractions and relaxations of the airway smooth muscle. The increased parasympathetic activity could act as a compensatory response to the sympathetic stimulation associated with frequent and intense training. This could induce not only the resting bradycardia but also an increase in bronchomotor tone and, in turn, an increased susceptibility to the development of asthma [6]. A dysfunctional neuroendocrine–immune interface may then play a role in the pathogenesis of EIB, mainly due to release and action of neuropeptides from primary sensory nerve terminals, in a so-called neurogenic inflammation pathway. This is also clinically supported by a positive effect of inhaled ipratropium bromide in athletes with EIB. A previous study in children has shown an association between the degree of response to treatment with the anticholinergic drug and the vagal activity, suggesting the therapeutic effect may be related to an individual patient's vagal activity [7].

> **"...multiple asthma phenotypes exhibiting differences in clinical response to treatment exist and assessment should be multidimensional..."**

Increased circulating levels of substance P, one of the major initiators of neurogenic inflammation, have been found after strenuous exercise [8]. This probably results from the upregulation of the *PPT-1* gene, from which substance P is derived, and NK-1 receptors. This explanation is in part supported by the study of Teixeira and colleagues [9]. These authors systematically compared the behavioral and immunological effects induced by substance P and swim stress in mice and investigated the participation of the NK-1 receptor on the modulation of these effects [9]. They demonstrated that antagonism of the NK-1 receptor inhibited the stress effects of swim stress and that injection of substance P in mice showed similar stress effects as swim on ethological parameters [9]. Nevertheless, in humans, the role of neurogenic airway inflammation in the pathogenesis of either EIA or EIB has been poorly studied and it is not restricted to the neurokinins.

Members of the transient receptor potential (TRP) superfamily of ion channels play a key role in the response of sensory neurons to inflammatory mediators and noxious chemical stimuli, initiating respiratory depression, cough, glandular secretions and other protective responses [10]. Jordt *et al.* recently suggested that TRPA1 may function as an integrator of chemical and immunological stimuli modulating inflammation in the airways [10]. Furthermore, chemical irritant-induced activation of TRPA1 may trigger the release of neuropeptides and chemokines in the airways, thereby exacerbating the cellular and tissue inflammatory response observed in allergic individuals [11]. The question remains of whether a similar mechanism could occur in athletes exposed to irritants, such as those resulting from disinfection products used in swimming pools and others when training outdoors, independent of their atopic and asthma status.

In Belgian schoolchildren, cumulated pool attendance has been related with asthma prevalence, EIB and, in a dose-dependent manner, with markers of lung epithelium damage [12]. These data led to the idea of higher rates of sensitization and atopic diseases after easier penetration of aeroallergens by damaged airway epithelium. Studies in athletes are in line with this observation. Helenius *et al.* have reported increased levels of eosinophils and neutrophils, as well as increased concentrations of sputum eosinophil peroxidase and human neutrophil lipocalin in induced sputum from swimmers [13]; Sue-Chu *et al.* reported lymphoid aggregates in endobronchial biopsies from skiers [14], suggesting increased airways inflammation due to training as well as a wear-and-tear effect caused by increased ventilation during endurance training [15].

Genetic susceptibility, neurogenic-mediated immune inflammation and epithelial sensitivity appear to be mechanisms that should be taken in account when explaining the athlete's individual risk for bronchoconstriction. Further studies should better define the etiologic factors and mechanisms involved in the development of asthma in Olympian athletes, and propose relevant preventive and therapeutic measures.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Schwartz LB, Delgado L, Craig T *et al.* Exercise-induced hypersensitivity syndromes in recreational and competitive athletes: a PRACTALL consensus report (what the general practitioner should know about sports and allergy). *Allergy* 63(8), 953–961 (2008).

2 Haahtela T, Malmberg P, Moreira A. Mechanisms of asthma in Olympic athletes – practical implications. *Allergy* 63(6), 685–694 (2008).

3 Carlsen KH, Anderson SD, Bjermer L *et al.* Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. *Allergy* 63(4), 387–403 (2008).

4 Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is. *J. Allergy Clin. Immunol.* 106(3), 453–459 (2000).

5 Park C, Stafford C, Lockette W. Exercise-induced asthma may be associated with diminished sweat secretion rates in humans. *Chest* 134(3), 552–558 (2008).

6 Filipe JA, Falcao-Reis F, Castro-Correia J, Barros H. Assessment of autonomic function in high level athletes by pupillometry. *Auton. Neurosci.* 104(1), 66–72 (2003).

7 Knopfli BH, Bar-Or O, Araujo CGS. Effect of ipratropium bromide on EIB in children depends on vagal activity. *Med. Sci. Sport Exer.* 37(3), 354–359 (2005).

8 Lind H, Brudin L, Lindholm L, Edvinsson L. Different levels of sensory neuropeptides (calcitonin gene-related peptide and substance P) during and after exercise in man. *Clin. Physiol.* 16(1), 73–82 (1996).

9 Teixeira RM, De Lima TCM. Involvement of tachykinin NK 1 receptor in the behavioral and immunological responses to swimming stress in mice. *Neuropeptides* 37(5), 307–315 (2003).

10 Bessac BF, Jordt SE. Breathtaking TRP channels: TRPA1 and TRPV1 in airway chemosensation and reflex control. *Physiology (Bethesda)* 23, 360–370 (2008).

11 Caceres AI, Brackmann M, Elia MD *et al.* A sensory neuronal ion channel essential for airway inflammation and hyperreactivity in asthma. *Proc. Natl Acad. Sci. USA* 106(22), 9099–9104 (2009).

12 Bernard A, Carbonnelle S, Dumont X, Nickmilder M. Infant swimming practice, pulmonary epithelium integrity, and the risk of allergic and respiratory diseases later in childhood. *Pediatrics* 119(6), 1095–1103 (2007).

13 Helenius IJ, Rytila P, Metso T, Haahtela T, Venge P, Tikkanen HO. Respiratory symptoms, bronchial responsiveness, and cellular characteristics of induced sputum in elite swimmers. *Allergy* 53(4), 346–352 (1998)

14 Sue-Chu M, Karjalainen EM, Altraja A *et al.* Lymphoid aggregates in endobronchial biopsies from young elite cross-country skiers. *Am. J. Respir. Crit. Care Med.* 158(2), 597–601 (1998).

15 Carlsen KH. Asthma, airway inflammation and epithelial damage in elite athletes. *Eur. Respir. J.* 33(4), 713–714 (2009).