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Original research article

A similar pro/anti-inflammatory cytokine balance is present in the airways of competitive athletes and non-exercising asthmatics

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ABSTRACT

Purpose: Intensive exercise modifies airway inflammation and infection susceptibility. We aimed to determine the effect of exercise on pro- and anti-inflammatory cytokine (TNF-α, IL-1ra, IL-10) and innate immunity protein (HSPA1, sCD14) levels in exhaled breath condensate (EBC) and nasal secretions of competitive athletes, non-exercising asthmatics and healthy controls (HC).

Material and methods: The study group consisted of 15 competitive athletes (five speed skaters and ten swimmers) aged 15–25. The control groups comprised 10 mild-to-moderate asthmatics (AC) and seven HC. Athletes were assessed in- and off-training while asthmatics and controls at one time point. Nasal lavages and EBC were collected before and after a treadmill exercise challenge. Protein levels were assessed using ELISA.

Results: TNF-α levels in EBC were significantly higher in athletes than HC, but similar to asthmatic patients. In contrast, IL-1ra EBC concentrations were significantly lower in athletes than in HC, but again similar to asthmatics. Significant positive correlations were seen between baseline concentrations of TNF-α in EBC and fall in FEV1 following exercise challenge in athletes during training period ($R = 0.74$, $p < 0.01$) and in asthmatics ($R = 0.64$, $p < 0.05$). In nasal secretions, baseline IL-1ra levels were significantly higher in athletes and asthmatics than in HC. Exercise caused a slight, yet significant, increase in EBC HSPA1 in athletes ($p = 0.02$). The exercise challenge did not considerably influence TNF-α, IL-1ra, HSPA1 and sCD14 in EBC or nasal secretions.

Conclusions: Dysregulation of the TNF-α/IL-1ra balance in EBC and nasal secretions from athletes may reflect the presence of airway inflammation induced by repeated strenuous exercise.

1. Introduction

Regular physical exercise modifies the immune response depending on training level and frequency [1]. Strenuous exercise is believed to increase the prevalence of symptoms of respiratory tract infections (RTI) in regularly training subjects [2,3]. Nevertheless, microbial pathogens could be identified in less than one-third of cases of RTI-like symptoms [4] suggesting that non-infectious inflammatory factors could be responsible [1]. This airway inflammation may be further enhanced by unfavorable ambient conditions during exercise [5–8]. Exercise-induced bronchoconstriction (EIB) is almost an inherent feature of asthma, although it may occur as an isolated phenomenon in otherwise asthma-free subjects following exercise [9]. Local and systemic inflammation is important in the temporary narrowing of the airway associated with exercise [10–14]. The influence of exercise on the respiratory mucosa has been studied in a number of studies testing the concentrations of multiple mediators in exhaled breath condensate (EBC) or nasal lavage fluid (NLF) as a reflection of innate and inflammatory response [12,14–17]. Changes in the serum levels of innate immunity proteins are known to occur in professional athletes during the training season, in response to exercise load and ambient training conditions; similarly, serum levels of interleukin-1 receptor antagonist (IL-1ra) and heat shock protein HSPA1 increase in outdoor speed skaters during winter training, and serum IL-1ra and airway hyperreactivity are influenced on a long-term basis by the weather in the training area [6].

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Data concerning the influence of exercise on mediators of inflammation and innate immunity in the upper and lower airways is limited. TNF-α is a well-known pleiotropic pro-inflammatory cytokine released by a wide spectrum of cells. Its mRNA and protein levels are increased in asthmatic airways. Moreover, mast cell-derived TNF-α has been postulated as playing a role in the pathophysiology of airway smooth muscle contraction (as reviewed in [18,19]). A bout of exercise induces a peripheral increase of TNF-α, followed shortly by a secondary release of interleukin 10 (IL-10) and IL-1ra. These two interleukins are believed to have anti-inflammatory and immunomodulatory properties, and their plasma concentrations have been found to decrease in infection-prone subjects following exercise [2]. CD14 is a receptor for bacterial lipopolysaccharide (LPS) and is regarded as a marker of monocyte activation. HSPA1 is a "danger signal" for innate immunity mechanisms associated with natural killer (NK) cells and monocyte activation. Acute exercise has been described as a stimulus used to increase circulating heat shock protein levels [20].

The current study hypothesizes that the profile of inflammatory and innate immunity cytokines present locally in the upper and lower respiratory mucosae of competitive athletes resembles that present in the airways of non-exercising asthmatics. Therefore, the study compares the levels of three selected pro- and anti-inflammatory cytokines, i.e. tumor necrosis factor- α (TNF-α), interleukin 1 receptor antagonist (IL-1ra) and interleukin 10 (IL-10), and those of two innate immunity proteins, i.e. heat shock protein A1 (HSPA1) and soluble form of CD14 particle (sCD14), in the EBC and nasal secretions of competitive athletes, non-exercising asthmatics and healthy controls. In addition, the influence of acute exercise on the above parameters was studied with an aim to correlate the baseline levels of proteins with lung function parameters and exercise load in training.

2. Methods

2.1. Participants and study design

The study group consisted of 15 competitive athletes (five speed skaters and 10 swimmers) aged 15–25 years. The control groups comprised 10 mild-to-moderate asthmatics (asthma controls, AC) aged 19–39 and seven healthy, non-smoking subjects aged 21–27 (healthy controls, HC). The asthmatic subjects were recruited from the patients treated at the outpatient clinic of the Department of Allergology. The healthy control (HC) group comprised volunteering medical students and doctors. The exclusion criteria comprised any signs or symptoms of respiratory infection on assessment days and/or within four weeks beforehand, assessed according to the patient's reported history.

The clinical characteristics and exercise load data of the participating subjects are presented in Table 1. Median asthma duration in AC subjects was 4.5 years (range: 1–28 years). All asthmatics were fully controlled on inhaled corticosteroids (428 ± 66 μg budesonide equivalent, mean ± SE). Among the athletes, 11 (73.3%) had never been diagnosed with allergy, four (26.7%) had allergic rhinitis and one (6.67%) had been diagnosed with asthma. Symptoms of respiratory discomfort were self-reported by 66.7% (chest tightness/wheeze) and 53.3% (shortness of breath/cough) of athletes. Five athletes (33.3%) reported symptoms of rhinitis and one (6.67%) conjunctivitis.

Speed skaters and swimmers were competitive athletes performing at national level in their respective disciplines. They had been training on a regular basis for at least three consecutive seasons at the moment of recruitment into the study. To avoid possible selection bias, all athletes from local speed skating club and academic swimming section were invited to the study without presenting any incentive for those self-suspecting asthma or allergy or having been diagnosed with either condition. The athletes were assessed at two time points: Firstly, during a period of more intensive training and participation in competitions (training period, TP), and secondly, when the exercise performed was less typical for a given discipline and no participation in competition tournaments was required (off-training period, OTP). However, the one-week and four-week periods preceding the assessment had similar overall exercise loads (Table 1). The TPs for skaters lasted from January through March, and for swimmers from June through to the beginning of October. OTPs were from May through July for speed skaters and late autumn and winter for swimmers. The usual training regimen for both speed skaters and swimmers, irrespective of season, typically included a daily three-hour session, six days a week. Assessments were carried out at both time points (i.e., TP and OTP) during normal training activity and no abstention from exercise was required. In most cases, previous training activity took place in the afternoon of the preceding day. Ten athletes (three skaters and seven swimmers) were assessed during both periods. One skater and three swimmers were seen during OTP and one skater during TP only. AC and HC were assessed at one time point during late summer or early autumn 2014; in addition, a lifestyle assessment in terms of regular physical activity was also performed based on declarations by the subjects.

Table 1
Clinical and exercise load characteristics of the studied groups. Medians with interquartile ranges in parentheses are given unless indicated otherwise. *$p < 0.05$ versus HC; ND, not done.

	Athletes training period (TP)	Athletes off-training period (OTP)	Asthmatic controls (AC)	Healthy controls (HC)	P (Kruskal-Wallis ANOVA)
No. subjects (males/females)	11 (6/5)	14 (10/4)	10 (6/4)	7 (4/3)	ND
Age [years]	18 (15–20)	19 (16.5–20)	26 (21.5–34)	24 (23–26)	<0.0001
FEV1 [%predicted]	112 (107–125)	115 (109.5–123.3)	103.5 (96.75–111)	109 (107–113)	0.08
FEV1/FVC	0.84 (0.71–0.89)	0.83 (0.72–0.90)	0.82 (0.77–0.89)	0.84 (0.80–0.90)	0.97
IPAQ 1 week [MET-h/week]	8166 (4692–11679) *	9443 (5340–12980) *	3212 (1496–6645)	1236 (676–1920)	0.0067
Mean IPAQ 4 weeks [MET-h/week]	7566 (5724–11071) *	9657 (4875–12085) *	3786 (1686–7105)	1236 (1052–3252)	0.0027
No. atopics (%)	2 (18.2)	3 (21.4)	10 (100)	0 (0)	ND
No. positive exercise challenges (%)	2 (18.2)	1 (7.14)	5 (50)	0 (0)	ND
Percent FEV1 decrease during exercise challenge [geometric mean with range]	4.11 (1.49–19.35)	3.56 (1.02–17.28)	4.18 (0.38–22.68)	2.89 (0.39–7.65)	0.93