

Airway inflammation and upper respiratory tract infection in athletes: is there a link?

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ABSTRACT

Upper Respiratory Tract Infection (URTI) is regarded as the most common medical condition affecting both highly trained and elite athletes, in particular those participating in endurance events. The causes of these disturbances, also occurring during training, remain unclear. Viruses such as rhinovirus, adenovirus and para-influenza virus are frequently reported as the source of URTI. However, in a few comprehensive laboratory and epidemiological studies which reported at least a 30% incidence of URTI, no identifiable pathogens were either reported or studied. A recent, longitudinal study investigated symptomatology and pathogenic etiology in sedentary controls, recreational and elite athletes. The highest incidence of URTI occurred in elite athletes. However, only 11 out of 37 illness episodes overall had pathogenic origins, and most of the unidentified upper respiratory illnesses were shorter in duration and less severe than infectious ones. This concept of inflammation without infection in athletes is quite new and leads us to consider other explanatory pathophysiological conditions. Increases in airway neutrophils, eosinophils and lymphocytes have been described under resting conditions in endurance sports, swimmers and cross-country skiers. These inflammatory patterns may be due to pollutants or chlorine-related compounds in swimmers. After intense exercise similar airways cellular profiles have been reported, with a high amount of bronchial epithelial cells. This increase in airway inflammatory cells in athletes can result from a hyperventilation-induced increase in airway osmolarity stimulating bronchial epithelial cells to release chemotactic factors. Fortunately, in most cases, these inflammatory cells express rather low level of adhesion molecules, explaining why airway inflammation may appear blunted in athletes despite numerous inflammatory cellular elements. However, it can be hypothesized that a transient loss of control of this local inflammation, due to various external physico-chemical strains, might occur. This might account for some of the unidentified upper respiratory illnesses.

Keywords: airway inflammation, environment, sports, upper respiratory tract infection

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The aim of this short review is to provide an up-to-date summary of the known effects of exercise on airway inflammation and upper respiratory tract infections. Although additional research is needed, there are some consistent data in the existing literature allowing these two topics to be tentatively linked.

1. Airway inflammation in athletes: cellular aspects

Many studies about airway inflammation in athletes reported an increased number of inflammatory cells in bronchial biopsies, bronchioalveolar lavage fluid (BALF) or induced sputum of endurance athletes of different sports measured at rest (see ref 5 for review).

When compared with sedentary controls, cross-country skiers show increased total cell and lymphocyte counts in BALF (39), lymphoid aggregates (37) and increased T-lymphocytes, macrophage, eosinophils, neutrophils in endobronchial biopsies (21). Similarly, runners show increased cellularity and marked neutrophilia but no increase in eosinophils or lymphocytes in induced sputum (3). Elite swimmers show increased neutrophil and eosinophil counts in induced sputum (20). Interestingly, swimmers training outdoors have increased numbers of neutrophils in induced sputum, but no associated eosinophilia (25). Because the increase in neutrophils is observed in all the above sports, this may be a direct consequence of endurance training. In contrast, the increase in eosinophil and lymphocyte counts is likely to be related to the exposure to environmental factors, such as chlorine compounds in swimmers or dry air and cold air in cross-country skiers (5). The mixed type eosinophilic and neutrophilic airway inflammation shown by ice-hockey players is peculiar and more complex since these athletes are chronically exposed to both cold and dry air and carbon and nitrogen oxides from ice resurfacing machine in indoor ice arenas (18)

Airway inflammation and asthmatic symptoms improve in swimmers quitting competitive training, but tend to worsen in those who continue their sport career (19).

Very few studies about effect of acute exercise on airway cell changes are available. Bronchial cell counts are unaffected by 5-km swimming in an open swimming pool whereas the same distance swum in the sea slightly increases airway eosinophil differential counts (4). The same group reported increased neutrophils in sputum after a marathon and an all-out rowing test in non asthmatic athletes (3, 24). High counts of airway macrophages are also reported post-exercise in rowers (24).

2. The concept of blunted airway inflammation

In spite of elevated numbers of inflammatory cells in the BALF, sputum or bronchial biopsies, markers of inflammation such as eosinophil peroxidase, neutrophil lipocain or elastase were generally found at normal or very slightly increased concentrations at rest or after exercise in cross-country skiers, runners or outdoor swimmers (3, 5, 25).

Exercise-induced hyperventilation is responsible for both cooling–rewarming process (15, 16) and epithelial cell dehydration (especially if exercise is performed in cold and dry air) and subsequent hyperosmolar cellular stress (2).

These two conditions induce a release of IL-8 and RANTES (Regulated on Activation, Normal T-Expressed and Secreted), two potent chemotactic agents, by the bronchial epithelial cells, suggesting a possible mechanism for exercise-induced leukocyte migration into the airways.

At this point, the airway neutrophil plays a pivotal role. Indeed, it has been shown in runners, swimmers, and rowers that expression of L-selectin by airway neutrophils decreases after exercise and no increase in the expression of CD11b/CD18 is observed (3, 4, 24). This attests to an absence of neutrophil activation. Airway macrophages and eosinophils also decrease their surface expression of the adhesion molecules LFA-1, L-selectin and MAC-1 respectively, following an all-out rowing test (24).

Considering the central role of neutrophil in potential airway inflammation, it is suggested that there is a modulation of neutrophil function by exercise hyperventilation, through airway hyperosmolarity and a shedding of L-selectin.

Therefore, the concept of “blunted inflammation” (13, 35) originally developed to characterize the low-grade systemic inflammatory status after regular training (40) might be applicable to the upper respiratory tract as well.

Little is known about airway cytokine expression during or after exercise. However, Cox et al. (6) recently conducted an interesting study, comparing plasma cytokine levels at rest and post exercise, in healthy (less than 2 URI per year) and illness-prone (more than 4 URI per year) athletes. In illness-prone athletes they observed lower absolute concentrations of IL-10, IL-1ra, and IL-8, at rest combined with a greater post-exercise elevation in IL-6: this highlighted a potential for excessive inflammatory responses. The altered state of inflammatory control observed in this group might explain the increased rate of URI in these individuals. It is important to confirm with additional experiments whether or not these altered plasma cytokine profiles also exist at the airway level. Such research would help in understanding whether or not illness-prone athletes show different local cytokine profiles compared with healthy athletes within and without upper respiratory episodes.

3. Airway inflammation: environmental aspects

Swimmers may represent the most interesting population when studying upper respiratory symptoms, inflammation and environmental aspects (31). When swimming for up to 30 hours per week, competitive swimmers inhale large amounts of air immediately above the water surface and are exposed to large quantities of chlorine derivatives from swimming pool disinfectants (32). When compared to sedentary and healthy controls, elite swimmers demonstrated higher levels of exhaled leukotriene B₄, attesting to a neutrophilic and eosinophilic inflammation, possibly accounting for airway tissue damage. Such chronic exposure is frequently (36% to 79% in competitive swimmers), associated with bronchial hyperresponsiveness (22) and asthma (33%; 41). However, in swimmers who stop high-level training, bronchial hyperresponsiveness and asthma may attenuate or even disappear, whereas mild eosinophilic airway inflammation is aggravated among highly trained swimmers who keep on training hard (19).

Competitive Nordic skiers are also regularly exposed to environmental thermal and hygro-metric stress. Karjalainen et al. (21) submitted elite nordic skiers to

methacholine provocation test, bronchoscopy and bronchoalveolar lavage. Bronchoscopy and bronchoalveolar lavage of these skiers revealed evidences of airway remodelling and thickening which were the same for both those with and without bronchial hyperresponsiveness to methacholine. This clearly indicated that the observed structural changes were a general consequence of chronic hyperpnoea of cold, dry air. This specific pattern of inflammation independent bronchial hyperresponsiveness, so-called “skier’s lung”, included a slight increase of neutrophils, tumour necrosis factor alpha and myeloperoxidase, as well as increased numbers of mast cells and lymphocytes (39). This pattern was much less influenced by budesonide treatment than by the hydration and osmotic status of the respiratory mucosa (38). Interestingly, Davis et al (9), using a canine model of dry air challenge, showed that a single hyperventilation challenge induced extensive but reversible mucosal injury and neutrophilic inflammation that was not completely resolved one week after the challenge. Since the trigger factors, the clinical features, and the time course are similar, it is thus tempting to associate such phenomenon with the unidentified-URI (36), at least for endurance athletes exercising in cold environments.

4. Upper Respiratory Tract Infection in Athletes

Numerous studies have shown an inverse relationship between decreased immune function and augmented exercise workloads (7, 8, 17, 23, 27). Very few studies have actually been able to show a direct link between exercise-induced immune depression and increased incidence of confirmed illness in athletes. Nevertheless, it is important to note that acute URTI is the most frequent reason for consultation in sports medicine clinics (11), and is the most common medical condition affecting athletes attending both summer and winter Olympics (14, 34).

This relationship between training status and susceptibility to infection has been modelled in the form of a “J”-shaped curve (28). This suggests that, while engaging in moderate activity may reduce the incidence of illness sedentary levels, excessive amounts of prolonged and high-intensity exercise may result in an increased incidence of illness. Some epidemiological studies confirmed that athletes engaged in intensive endurance training appear to be more susceptible to URTI than their moderately active peers. Examining illness patterns in a cohort of 530 male and female runners who completed a monthly log for 12 months, Heath et al. (17) reported [that the odds of getting a URTI was] 2.00, 3.50, and 2.96 for running mileage between 486-865 miles, 866-1388 miles, and greater than 1388 miles, respectively. These results suggested that high running mileage is a significant risk factor for URTI.

Many concepts and some experimental data are now available to explain how intense regular physical training may increase the susceptibility to URTI (most of them virally-induced). In terms of immune function, intense exercise is known to decrease the expression of toll-like receptors and to increase cortisol, epinephrine, and IL-6 production. This leads to an impaired cell-mediated immunity and inflammation, via a decreased macrophage and Th-1 cell cytokine production (13).

Acute and exhaustive exercise (lasting more than three hours) also appears being a risk factor for increased URTI incidence.

For instance, Peters and Bateman (29) reported for the first time an increased URTI risk during the two weeks following the Capetown or Pretoria ultramarathons. This was later confirmed by other studies (26, 30) which reported a 100–500% increase in risk of picking up an infection in the weeks following a competitive ultra-endurance running event.

A more recent study (10) failed to confirm these findings in a large cohort of marathon runners where there was no difference in infection incidence in the 3 weeks after the race compared with the 3 weeks before. These authors reported that the post-race URTI incidence in runners without URTI symptoms in the 3 wk preceding the race was 16% and not statistically different from the 17% prerace URTI incidence. However, among the group of runners who experienced an URTI episode in the 3 weeks before the race, 33% experienced an URTI episode after the race also. This suggests that the stress of the exercise may have allowed a reactivation of the virus responsible for the pre-race infection or an extended duration of the infection when the latter occurred within the few days before the marathon.

However, most of the above cited studies did not clinically confirm infections. In view of this, it cannot be ruled out that some of the reported symptoms (e.g., sore throat) were caused by non-infectious airway inflammation due to drying of the mucosal surfaces and/or the inhalation of dry air, pollutants, or bronchial hyperresponsiveness.

5. The non-infectious hypothesis

Recently, Spence et al. (36) conducted a surveillance study over a 5-month summer/autumn competition season to identify the pathogenic etiology and symptomatology of upper respiratory illness (URI) in highly trained elite athletes ($n = 32$), recreationally competitive athletes ($n = 31$), and untrained sedentary controls ($n = 20$). These authors preferred to use the term “upper respiratory illness” rather than “upper respiratory infection”; the first definition being more general making thus possible the inclusion in such a definition of non-infectious episodes. When subjects presented two or more defined URI symptoms, they were administered the Wisconsin Upper Respiratory Symptom Survey (WURSS-44) questionnaire (1) to assess the daily symptomatology and functional impairment. Nasopharyngeal and throat swabs were collected on these subjects and analyzed using microscopy, culture, and polymerase chain reaction testing for bacterial, viral, chlamydial, and mycoplasmal respiratory pathogens. A total of 37 URI episodes in 28 subjects were reported (9 controls, 7 recreationally competitive exercisers, and 21 elite athletes). Although the overall distribution mimicked the “J”-shaped curve, with rate ratios for illness higher in both the control and elite cohorts compared with the recreationally competitive athlete cohort, only 11 infectious agents out of these 37 episodes (30%), were identified (2 control, 3 recreationally competitive exercisers, and 6 elite athletes). No pathogens were identified in 26 episodes of URI, leading to the non-infectious hypothesis drawn by these authors. This ratio is also confirmed by other similar studies (33) which have reported over 55% of illnesses without an identifiable pathogen.

However, the fact that no identifiable pathogen was observed does not necessarily mean that the URI is not infectious. Indeed, pathogens may not be detect-

ed in a relatively large proportion of patients with respiratory disease, because of limitations of current diagnostic assays, non-optimal timing of the detection period, or simply because some infections are caused by as yet unknown pathogens. For instance, systematic Epstein-Barr virus or other herpes viridae DNA analysis should systematically be undertaken in such study protocols since some of the unidentified URI symptoms might be associated with latent viral shedding (12).

Comparing the WURSS-44 specific global symptom, total symptom, and functional impairment severity scores in URI and unidentified URI (no identifiable pathogen) groups, Spence et al (36) reported similar scores within the first two days but higher in subjects of the URI group, particularly on illness days 3–5. Moreover, the episode duration was about 3 days longer in the URI group (9.6 +/- 2.4 d vs 6.5 +/- 3.2 d; $p < 0.006$). These findings suggest that there may have been a higher degree of immunological and inflammatory activation in those cases where a pathogen was identified.

Measuring systemic and local (upper respiratory tract) biological indices of inflammation or immune activation in future studies is important. Indeed, this may help to differentiate symptoms caused by pathogen agents from those caused by inflammatory, allergic, cold dry air inhalation, vasomotor, and other idiopathic upper respiratory disorders seen in athletes.

Conclusion and future developments

Cellular components of airway inflammation exist in high-level athletes airways, particularly those involved in endurance events. These airway cellular patterns may differ according to: a) the type of sports, b) the environmental conditions, c) the duration of sports career, and d) the existence of allergy. However, despite these numerous inflammatory components, airway inflammation usually appears as a tightly regulated and blunted process, as it can be seen with the low grade systemic inflammation encountered after regular training. The most attractive hypothesis includes a modulation of the high amount of airway neutrophils by exercise hyperventilation, through an airway hyperosmolarity. This hyperosmolarity would trigger both release of neutrophilic chemotactic factors and shedding of adhesion molecules. This antagonism would maintain a low level of local inflammation and preserving athlete's respiratory health.

Whether or not a transient imbalance in these opposed influences may explain some of the so called “non infectious upper respiratory episodes” deserves more investigations. Moreover, the respective contribution of regular cold dry air inhalation, cellular lineage dehydration, pollutants (especially chlorine-related compounds) exposure to these non-infectious episodes should be studied in more detail. In order to obtain a better diagnosis, treatment, and management strategies of upper respiratory episodes in athletes, the following research axes should be considered:

- Confirm the existence of infectious or non-infectious upper respiratory episodes, by improving i) pathogen detection methods (including systematic EBV DNA quantification in order to identify serological reactivation) and timing of these detections when a supposed URTI occurs, ii) clinical monitoring (e.g. pulse, temperature, symptom scores, and clinical examination) of these episodes, iii) characterisation of the studied population:- e.g. type of sports,

environmental factors, training parameters, allergic and immunological status.).

- Develop an airway osmotic stress test and use it routinely, especially when investigating endurance athletes exposed to cold and dry environments
- Look for more indices of systemic inflammation (e.g., cytokine profiles, ultra sensitive measurement of C-reactive protein), especially in the case of suspected non-infectious upper respiratory episodes. This would help understanding whether or not unidentified URI could have an echo at the systemic level and to which extent this could influence scores of respiratory symptom questionnaire.
- Conduct more studies at the airway level, in order to compare: i) cell population and distribution, ii) chemotactic and cytokine factors, iii) adhesion molecule expression, in illness-prone versus healthy athletes, or infectious versus non infectious episodes.
- Test the hypothesis of exercise-induced airway inflammation as a risk factor of viral infection. Expression of dysfunctional adhesion molecules and ICAM-1 (Intercellular Adhesion Molecule-1) in the post-exercise situation could theoretically lead to a higher risk of URTI, with ICAM-1 being the major rhinovirus receptor.

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