

REVIEW ARTICLE

Mechanisms of exercise-induced bronchoconstriction in athletes: Current perspectives and future challenges

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Abstract

The evidence of exercise-induced bronchoconstriction (EIB) without asthma (EIBwA) occurring in athletes led to speculate about different endotypes inducing respiratory symptoms within athletes. Classical postulated mechanisms for bronchial obstruction in this population include the osmotic and the thermal hypotheses. More recently, the presence of epithelial injury and inflammation in the airways of athletes was demonstrated. In addition, neuronal activation has been suggested as a potential modulator of bronchoconstriction. Investigation of these emerging mechanisms is of major importance as EIB is a significant problem for both recreational and competitive athletes and is the most common chronic condition among Olympic athletes, with obvious implications for their competing performance, health and quality of life. Hereby, we summarize the latest achievements in this area and identify the current gaps of knowledge so that future research heads toward better defining the etiologic factors and mechanisms involved in development of EIB in elite athletes as well as essential aspects to ultimately propose preventive and therapeutic measures.

KEYWORDS

epithelial injury, neurogenic inflammation, osmotic, sports, thermal

1 | INTRODUCTION

It has long been recognized that physical exercise may induce respiratory symptoms in susceptible individuals.¹ In fact, exercise has been implicated as the most common trigger of an acute asthma attack among elite athletes who have been clinically diagnosed with asthma, and it has been documented that the airways of most individuals with asthma are hyper-responsive to exercise. Nevertheless, the term exercise-induced asthma (EIA) only became popular in the 1960s and 1970s when several reports addressed the pattern of airway response to exercise and the influence of drugs on EIA, particularly in children.¹⁻³

In the 1970s, the prevalent impression was that there was no evidence that EIA occurred in other patients rather than asthmatics,

and although sporadic cases had been reported where exercise appeared to be the only precipitant of asthma, careful investigation usually revealed other clinical and physiological manifestations of asthma.⁴ Later, however, the concept that exercise may induce bronchial obstruction only in asthmatic patients has been questioned.⁵ In fact, nowadays many experts advocate using the terminology “exercise-induced bronchoconstriction” (EIB) instead of EIA as it does not imply that the patient has underlying chronic asthma or that exercise actually “causes” asthma.⁶ EIB that occurs in athletes without other features of asthma has peculiar clinical and pathologic features. Accordingly, some authors started to consider it as a distinct phenotype.⁷ Several elite athletes who are diagnosed with EIB have neither personal nor family history of asthma, suggesting that in such cases environmental factors are more important than genetic

inheritance. At rest, they seldom experience asthma symptoms,⁸ which rather occur during high-intensity exercise. So, accordingly, we proposed designating EIB with asthma (EIB_A) the occurrence of bronchial obstruction after exercise in asthmatic athletes, and EIB without asthma (EIBw_A), the occurrence of bronchial obstruction induced by exercise in athletes without other symptoms and signs of clinical asthma.

Previously, the possibility of two different phenotypes among athletes has been suggested: the pattern of "classical asthma" characterized by early onset of asthma in childhood, bronchial hyper-responsiveness (BHR) diagnosed by methacholine challenge, atopy and signs of eosinophilic airway inflammation; and another phenotype with onset of respiratory symptoms during sports career, BHR to eucapnic hyperventilation test (EVH) and a variable association with atopic markers and eosinophilic airway inflammation.⁹ More recently, using latent class analysis, Couto et al.¹⁰ identified two distinct phenotypes of EIB in athletes: "atopic asthma" defined by the occurrence of allergic sensitization, increased levels of exhaled nitric oxide, rhinitis and other allergic comorbidities; and "sports asthma", defined by the presence of exercise-induced respiratory symptoms and BHR in the absence of allergic features. Of note, these two phenotypes match with the proposed definitions of EIB_A and EIBw_A.

Moreover, it has been revealed that athletes practicing water and winter sports show an increased risk of "sports asthma",¹⁰ corresponding to EIBw_A. These are among sports with a higher prevalence of athletes with EIB,¹¹ which is consistent with the hypothesis of the sport practicing itself and the environmental conditions during training and competition influencing the occurrence of EIB.

Hereby, we identify the latest evidences regarding EIB in athletes so that future research in this area overcomes the current gaps of knowledge, to better define the etiologic factors and mechanisms involved in development of EIB in elite athletes.

2 | DEVELOPMENT AND RISK FACTORS FOR EIB IN ATHLETES

EIBw_A in athletes is thought to be the result of years of intensive training.¹² So far, only indirect evidence for this association has been provided.¹³⁻¹⁵ Alternatively, some elite athletes, such as elite swimmers, started sports at young age, which might result in several years of daily exercise with specific environmental exposure before becoming a professional athlete. This increases their risk to develop EIBw_A at young age or during their adolescence. Eucapnic voluntary ventilation (EVH) has been proposed as the gold standard to detect EIB in athletes, but more studies are needed to recommend EVH for screening of EIB in young athletes.¹⁶⁻¹⁹ The prevalence of EIB has been evaluated in young (12-14 years) elite swimmers by EVH but no significant increased prevalence in EIB was detected compared to age-matched controls, although the magnitude of the reduction in FEV₁ was higher in swimmers than controls.²⁰ A recent study compared young (12-14 years) swimmers, basketball, and football players

and found the highest prevalence of EIB in swimmers, but only small groups were analyzed.¹⁹

Longitudinal follow-up of young athletes is needed to unravel the mechanisms behind the development of de novo EIB in athletes throughout their sports career. Such studies might identify risk factors that are associated with EIBw_A and provide biomarkers that can early on predict occurrence of EIBw_A. The different prevalence of EIB between sports disciplines raises the possibility that exercise per se, or even repeated increased ventilation, may not be the only mechanism involved in the development of these conditions in athletes. EIB may be modulated by the baseline condition of the subject or by sport-specific characteristics. The level of exercise load is fundamental, and a kind of "biological gradient" may seem to occur, and can be evaluated by examining exposure time in a sport or cumulative hours of training and how this modifies the risk of airway dysfunction.^{21,22}

Environmental factors, involving the "type" and "content" of the ambient inhaled air, also play an important role,²³ while immune and neuronal influences could play a modulatory role. The quality of inspired air is dependent on the type of exercise (e.g. indoor/outdoor)²⁴ and sport-specific conditions (e.g. winter and water sports).¹ Extrinsic factors, together with intrinsic factors, can affect athletic performance.²⁵ It has long been recognized that atopy is positively associated with EIB and increased BHR in athletes.^{26,27} For instance, with pre-existent airway inflammation or BHR, such as in a patient with allergic asthma and consequent EIB_A, an amplification of these mechanisms should be expected; it has been proposed that exposure to allergens in the presence of microvascular leak and exudation of plasma, caused by epithelial injury induced by increased ventilation during exercise, may induce airway "sensitization".²⁸ This "passive sensitization" could occur in nonasthmatic athletes who are atopic because they are likely to have more mast cells and more mediators, and their microvasculature will probably be more permeable.²⁸ However, uncertainty remains regarding the relative contributions of these factors in explaining the high degree of bronchospasm seen in various populations of athletes.

Both training in a cold air²⁶ and swimming pool²⁷ environment had been previously identified as risk factors for EIBw_A and were recently confirmed.¹⁰ Another recent study evidenced that EIB was present in 60% of swimmers and 29% of cold-weather athletes compared to only 17% of nonathlete controls.²⁹ For athletes practicing water and winter sports, in addition to frequent episodes of prolonged hyperpnoea, their sports performance demands exposure to potentially sport-specific environmental noxious stimuli.^{22,25} Increased neutrophil counts in induced sputum from both swimmers and winter sports athletes have been observed, and interestingly, they were correlated with the number of training hours per week in both groups.¹³

Hyperpnoea with cold dry air represents a significant environmental stress to airways and it has been previously reported that exposure to cold air cause parasympathetic stimulation of airways, contributing to EIB.³⁰ It has been observed that during one competitive winter season, adolescent cross-country skiers develop signs of

inflammation (lymphoid follicles and deposition of tenascin) in their bronchial biopsies.³¹ Airway neutrophilia has been shown to be corticosteroid insensitive.³² In a placebo-controlled study, treatment with inhaled corticosteroids did not show any beneficial effect in cold air athletes.³³ Alternative strategies are therefore needed for treating EIB in these types of athletes.

The association between EIB in relation to indoor swimming facilities is likely the result of the chemical disinfectants used in pools and the poor air circulation in these indoor facilities. Competitive swimmers with allergic asthma show a mixed type of airway inflammation.³⁴ It has been argued that an increase in neutrophils is a consequence of endurance training and that increased eosinophils and lymphocytes result from exposure to a chlorine-rich atmosphere and microaspiration of water droplets related to the sport.^{20,35} It has been shown that swimming has the highest prevalence of BHR in comparison with the other aquatic disciplines and that endurance aquatic disciplines have a higher prevalence than the aquatic non-endurance disciplines.³⁶ The high prevalence of EIB among swimmers compared to the other aquatic disciplines points to other etiologic factor than only environmental exposure, such as training intensity, type, and/or duration.³⁶ This finding emphasizes the need for further research to determine the etiologic mechanism of EIBwA in swimmers including long-term follow-up studies.

The prevalence of EIB is highest also in athletes who are exposed to environments with high concentrations of particulate matter and/or gaseous irritants³⁷ (Table 1). The deposition of pollutants is greater during high-ventilation exercise by allowing more irritants to reach the distal airways. High levels of CO₂, NO₂, and ultrafine particles are often present in indoor ice rinks,³⁸ and a high prevalence of respiratory symptoms in ice-hockey players has been shown,^{39,40} as well as in speed skaters.⁴¹ Pollen, molds, and environmental pollutants may influence performances and the presence of EIB_A in allergic athletes practicing outdoor sports.²⁶ Pollution from traffic may influence air quality in athletic fields.⁴²

3 | MECHANISMS OF BRONCHOCONSTRICTION IN ATHLETES

Exercise-induced bronchoconstriction was initially proposed to be secondary to mediator release from mast cells.⁴³ More recently, however, it has been proposed that the refractory period observed after a positive exercise challenge may not be associated with decreased levels of the primary mediators of bronchoconstriction released from mast cells, but probably with the release of a protective prostaglandins, presumably PGE₂, and possibly the desensitization of the cysteinyl leukotriene receptor.⁴⁴ Injury to the airway epithelium, overexpression of cysteinyl leukotrienes, relative low protection of prostaglandin E₂, and greater airway eosinophilia have been found to be distinctive immunopathologic features of asthma with EIB, demonstrating an inflammatory basis of EIB.⁴⁵ A relationship between columnar epithelial cells in induced sputum and severity of EIB was shown, as well as an association between the

TABLE 1 Sports with different levels of EIB risk (adapted from Del Giacco et al.²¹)

Risk	Characteristics	Examples of sports
Low-risk sports	Sports in which the athlete performs a <5-8 min effort	Track and field: Sprint (100, 200, and 400 m) Middle distance (800 and 1500 m) Hurdles (100, 110, and 400 m) Jumps Throws Decathlon Heptathlon Tennis Fencing Gymnastics Downhill skiing Boxing Golf Body building Weightlifting Martial arts
Medium-risk sports	Sports in which the continuous effort rarely lasts more than 5-8 min	Soccer Rugby American football Basketball Volleyball Handball Baseball Cricket Field hockey
High-risk sports	Sports in which the athlete performs a >5-8 min effort and/or in a dry/cold air environment and/or in a noxious (chlorine exposure, ultrafine particles, traffic air pollution) air environment	Swimming Water polo Track and field: Long distance (5000 and 10000 m) 3000 m steeplechase Pentathlon (mixed) Walks (20 and 50 km) Marathon Cycling Cross-country skiing Ice hockey Ice skating Biathlon High-altitude sports

concentration of columnar epithelial cells with the levels of histamine and cysteinyl leukotrienes in the airways, confirming the role of mediators' release.⁴⁶ Although mediator's release does contribute

to EIB, pathophysiologic changes induced by intense exercising are definitely more complex. At present, it is widely accepted that it is likely multifactorial and is probably caused by exercise-induced increased ventilation and related changes in airway physiology. The increased ventilatory rate needed to meet the higher muscular oxygen requirements during exercise challenges the ability of the airways to condition the inhaled air to the correct moisture and heat levels before the air reaches the alveoli. Vigorous exercise results in the inhalation of increased volumes of relatively cold and dry air, resulting in key pathogenic events related to EIB: airway osmotic changes, epithelial injury, airway inflammation, and neuronal activation. Figure 1 summarizes the players in the pathophysiology of EIB.

Classical postulated mechanisms behind EIB include the "osmotic" and the "thermal" hypotheses. Both are based on the exercise-induced increased ventilation, which seems to be the most important factor inducing water loss and mucosal cooling and dehydration.²⁸ Due to the increased ventilation, the airway surface liquid becomes hyperosmolar as water is evaporated. Using a time-dependent mathematical model of the heat and water vapor transport in the human respiratory tract for mouth breathing, Daviskas et al.⁴⁷ concluded that contribution of each airway to the conditioning of inspired air was found to depend on the inspired air conditions and the pattern of breathing. The rate of water loss on the lower airways during hyperpnea was calculated at a much faster rate than in the resting state,⁴⁷ providing an osmotic stimulus for water to move from any cell nearby, which results in cell shrinkage and release of

inflammatory mediators that cause airway smooth muscle contraction and airway obstruction.²⁸ Airway cooling stimulates cholinergic receptors in the airways, increasing airway smooth muscle tone, and airway secretions.⁴⁸ During and mostly postexercise a rewarming process begins, as a physiological consequence of the previous cooling and cause secondary hyperemia, and by that increased permeability in capillaries, which contributes to a leakage of fluid from the capillaries to the submucosa.⁴⁹

Studies of airway pathology in athletes are scarce, but various investigators have documented increased levels of airway cellular inflammatory markers,^{39,50-52} increased eosinophils,^{34,53} neutrophils,^{15,31,34,51} and/or epithelial cells.¹³ Recently, an increased presence of damage-associated molecular patterns (DAMPs) in the sputum of athletes was demonstrated,¹⁵ which may act as early inducers of the pro-inflammatory cytokines. Interestingly, the inflammatory markers observed in athletes airways are not consistently related to lung function, BHR, or disease exacerbations.^{52,54-56} Studies on the effects of anti-inflammatory drugs such as montelukast⁵⁷ and inhaled corticosteroids^{33,58} in elite ice-hockey players and cross-country skiers have reported no beneficial or only partial effect on asthma-like symptoms, BHR, or airway cellular inflammation. Sue-Chu et al.³¹ showed that during one competitive winter season, adolescent cross-country skiers developed signs of inflammation in their bronchial biopsies whether they were asthmatic or not. Airway inflammatory cells are increased but not activated in athletes, both at rest and after exercise.³⁵ Therefore, it has recently been proposed

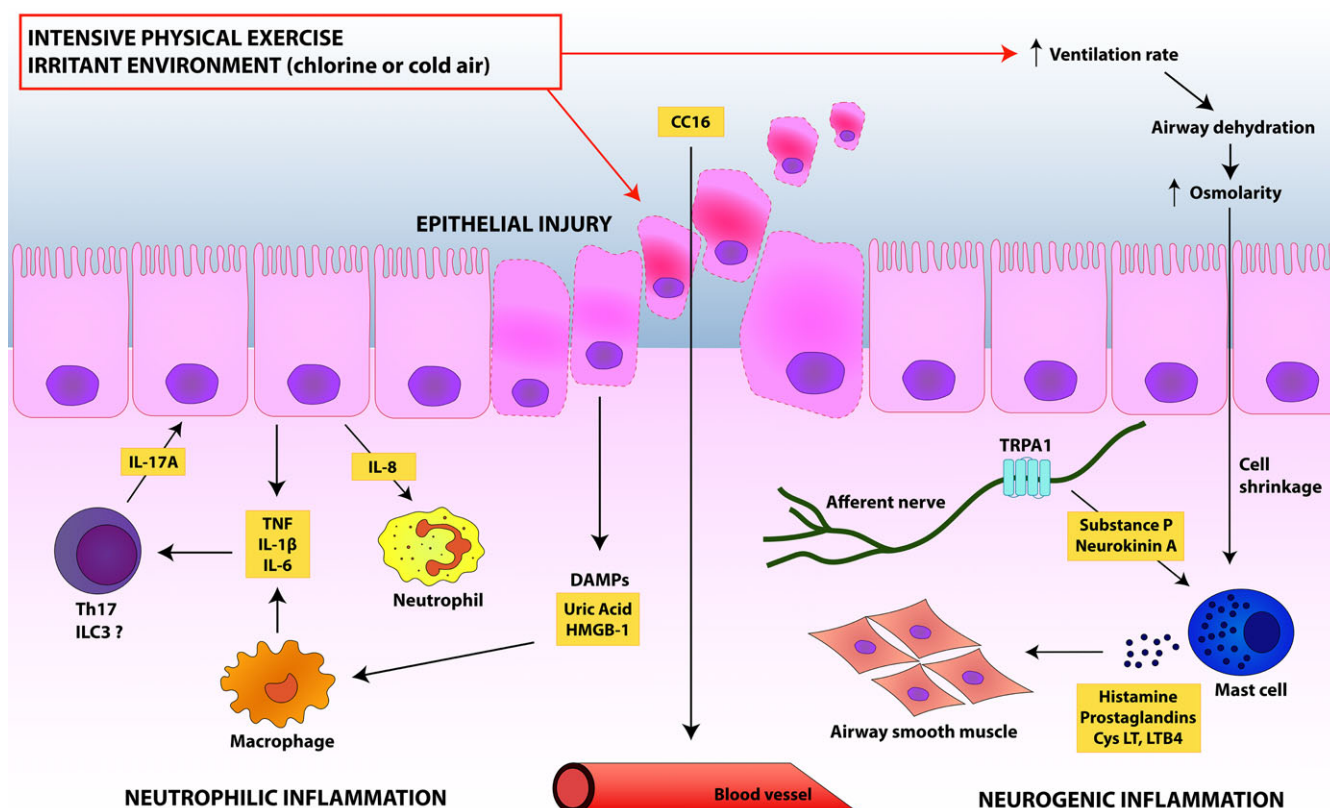


FIGURE 1 Emerging mechanisms of exercise-induced bronchoconstriction

that the increased airway inflammatory cells in athletes represent physical injury secondary to vigorous hyperpnea that heals with rest and may not be the initial factor implying detrimental effects on respiratory health.^{35,51,54,56,59,60} In accordance, it has been shown that although airway inflammation decreases after finishing competitive swimming, the prevalence of asthma diagnosis and use of medication increase significantly in both active and past adolescent swimmers, suggesting a relative independence of the two conditions.⁶¹

Emerging evidence indicates that injury to the airway epithelium caused by vigorous exercise is a key susceptibility factor for EIB^{28,45} (Figure 1). Injury of the distal airway epithelium was originally demonstrated after endurance training in half-marathon runners.⁶² The small-airway epithelium seems to be the most affected by damage and repair, as shown in mice studies.⁶³ Strenuous exercise characteristic of endurance sports is believed to have a detrimental effect on the respiratory epithelium structure, inducing a cascade of events that will favor bronchoconstriction.⁶⁴ The evidence to support this proposal comes from markers of airway epithelial injury.

Clara cell secretory protein 16 (CC16) is a peripheral marker for assessing the epithelial barrier injury in the lower airways. It has been previously shown that acute exercise induces epithelial stress by demonstrating that CC16 is increased after exercise in urine^{65,66} and in serum,^{15,62,67} as well as after eucapnic voluntary hyperventilation⁶⁸ in athletes. Whether the increase in airway osmolarity also induces an increase of urinary CC16 levels is not clear, as two studies investigating the effect of mannitol challenge showed conflicting results.^{66,69} In contrast to acute challenge, several studies revealed that baseline levels of CC16 in serum are considerably low in Olympic athletes⁷⁰; this chronic reduced presence of CC16, an anti-inflammatory factor, may additionally contribute to airway inflammation and hyper-responsiveness.⁷⁰

Besides the repeated training activity with high ventilation, also the environmental conditions could further contribute to increase both airways epithelial damage and inflammation. Swimmers are exposed to high levels of chlorine and chlorination by-products, such as trichloramine. A sudden increase in airborne trichloramine levels in an indoor swimming pool was associated with the presence of BHR in 85% of competitive swimmers.⁷¹ In accordance, it has been observed that acute exposure to these lung irritants produces an increase in CC16.⁷² However, serum CC16 in trained swimmers peak immediately after strenuous exercise, both in the copper/silver pool and in the chlorinated pool,⁶⁷ which raises the question about the relative role of trichloramines vs the epithelial injury induced by high ventilation.

It has also been shown that bronchial epithelial cells are released in higher amounts into sputum (epithelial shedding) of cold air athletes and swimmers¹³ highlighting the impact on epithelial layer. The high degree of persistent epithelial cell shedding is not associated with airway inflammation but suggested significant underlying airway injury.¹³ Moreover, a damaged airway epithelium might result in release of DAMPs in the airways of athletes¹⁵ as both bronchial epithelial cells and alveolar macrophages release DAMPs.

Although signs of injury to the airway epithelium have been observed at rest in swimmers¹³ and after half-marathon races in nonasthmatic runners,⁶² no such evidence was obtained at rest in cold air athletes¹³ or after a marathon in nonasthmatic runners.³⁵ The phenomenon of epithelial injury might be restricted to those athletes with proven EIB. Indeed, elite swimmers with a positive EVH test showed significantly increased sputum uric acid levels after EVH, while this was not seen in swimmers with a negative EVH test.¹⁵ Damage of the airway epithelium therefore potentially contributes to EIB in athletes, but additional research is needed. As previously shown, the distresses to the airway epithelial barrier induced by hyperpnea seem to be transient.⁶⁸ It is possible that periods with heavy training and periods with frequent and repeated competitions may maintain the epithelial damage as a stimulus for inflammation, but in periods with less heavy training the epithelium is restituted reducing the inflammatory stimulus.

One consequence of epithelial injury is replacement of ciliated epithelial cells by mucin-secreting cells and primarily goblet cells and athletes show more goblet cell hyperplasia and higher mucin expression than healthy or asthmatic subjects.¹⁴

An individual and exercise-specific etiologic factor for EIB in athletes may be the autonomic dysregulation associated with high-intensity and prolonged physical training. Cross-sectional studies show that endurance-trained subjects have higher parasympathetic activity than untrained subjects.⁷³⁻⁷⁵ The cholinergic-parasympathetic nerves stimulate bronchoconstriction, and in humans this is the predominant innervation at the bronchial level.⁴⁸ Intensive endurance training is believed to have an effect upon autonomic regulation promoting vagal activity predominance as a compensatory response to the sympathetic stimulation associated with frequent and intense training. The vagal hegemony induces the well-known resting bradycardia of athletes, but given that the parasympathetic system modulates airway tone, it is hypothesized that hyperactivity of that system would produce an increase in basal bronchomotor tone and contribute to BHR. Increased parasympathetic activity has previously been reported in endurance-trained athletes measured both by the parasympathetic activity of the eye by pupillometry in long distance runners^{74,75} and of the cardiovascular system by the variation in the heart rate induced by an exercise test.⁷⁶ Park et al.⁷⁷ found a relationship between BHR and a diminished sweat secretion, tearing and salivary flow rate in healthy athletes, indicating autonomic dysfunction. Furthermore, a significant correlation between heart rate variability indices and $\dot{V}O_2\text{max}$ was shown,⁷⁸ which suggests that endurance training and increased aerobic capacity are followed by increased parasympathetic activity. Recently, it has been shown significant correlations between parasympathetic parameters and PD_{20} methacholine in elite swimmers with clinically relevant BHR.⁷⁹ However, although the estimated parasympathetic tone seems to be higher in athletes, one study concluded that this parameter shows only a weak correlation with PC_{20} methacholine, suggesting that parasympathetic activity may act as modulator of airway responsiveness, but the increased prevalence of BHR in athletes may be related to the type and possibly the content of inhaled air during

training.⁸⁰ Stang et al.⁸¹ have also recently shown that the type of sport influences the relationship of BHR to parasympathetic activity.

The dysfunctional neuro-immune interface may also play a role in the pathogenesis of EIB due to a neurogenic inflammation pathway.⁸² Increased circulating levels of substance P, one of the major initiators of neurogenic inflammation, has been found after strenuous exercise.⁸³ Crimi et al.⁸⁴ demonstrated that bronchoconstriction induced by substance P may be due to cholinergic activation. Furthermore, it has been shown that acetylcholine released from the respiratory epithelium may have a stimulant effect upon airways inflammation.⁸⁵ Also, intense and prolonged physical exercise is associated with increased nerve growth factor serum levels in athletes.⁸⁶ It was recently showed, in a mouse model, that BHR can be induced by a single hypochlorite-ovalbumin instillation, independently of bronchial influx of inflammatory cell,⁸⁷ highlighting the role of transient receptor potential ankyrin 1 channel on nociceptive airway sensory nerves in nonallergic BHR.⁸⁷ These chemoreceptors are expressed on substance P-producing airway sensory nerve fibers and are involved in irritant-induced airway disease, and the activation of substance P receptor leads to bronchoconstriction.

In a broad and integrative perspective, the final model probably results from the interplay of all mentioned factors. The repeated heavy ventilation during endurance training acts as an early local respiratory injury inducing and maintaining airway inflammation and delaying epithelial repair. Inflammation is a nonspecific response of tissues to injury, which usually leads to repair and restoration of the normal structure and function. The restorative process after injury involves plasma exudation and movement of cells into the airways, a process repeated many times during a season of training.²⁸ This process has the potential to expose smooth muscle to a wide variety of plasma- and cell-derived substances. The exposure to these substances over time can lead to an alteration in the contractile properties of the smooth muscle and turn it more prone to bronchoconstriction. BHR is likely a result of both those structural airway changes, the so-called airway remodeling, and increased bronchial tonus related to higher parasympathetic activity. Research should follow this hypothesis and investigate whether drugs inhibiting bronchial parasympathetic activity, such as anticholinergics, are more effective for bronchodilation in athletes. These changes may be self-perpetuating by the frequent repetitive training sessions, but also stimulated by ambient environmental exposure where the sport is being performed.

4 | LONG-TERM EFFECTS OF SPORTS ON THE AIRWAYS OF ATHLETES

The development of BHR is known to increase with age.^{20,88,89} Of the 193 athletes competing at the 2006 Winter Olympics who met the IOC's criteria for approval of use of anti-asthmatic drugs in sports, only 32.1% had childhood asthma and 48.7% of athletes reported onset of EIBw_A at age 20 years or older.⁹⁰ Increased numbers of both eosinophils and mast cells were observed in bronchial

biopsies of competitive adult swimmers.¹⁴ These findings lead to the hypothesis that the relatively late onset of EIBw_A in many older athletes is related to the years of endurance training.¹¹ This hypothesis is supported by a recent study: Knöpfli et al.⁹¹ studied a small sample of seven athletes from the Swiss national triathlon team, who at baseline were characterized as nonasthmatic and who had performed at international level for at least three consecutive years. Three of seven developed EIB over a 2-year period. Additional longitudinal studies on bigger sample sizes are, however, required to confirm these data.

Two studies prospectively assessed long-term BHR and airway inflammation in swimmers.^{54,61} Helenius et al.⁵⁴ showed that BHR is reduced 5 years after finishing intensive swimming. In addition, both Couto et al. and Helenius et al.^{54,61} found that after follow-up, eosinophilic airway inflammation was aggravated among those swimmers who remained at high-level training and tended to attenuate in swimmers who finished their sports careers. In contrast to the effect of quitting sports for a long term, no significant change for swimmers' airway inflammatory cell counts was observed when comparing time points after intensive training or after training cessation for at least 2 weeks.⁹²

Our current knowledge of the natural history of EIBw_A in elite athletes is incomplete, and further studies are clearly needed to determine how many athletes will continue to experience EIB in the years after they cease intensive endurance training.¹¹

5 | FUTURE PERSPECTIVES

Genetic susceptibility, epithelial sensitivity, and neurogenic mechanisms should all be taken in account when explaining the athlete's individual risk of bronchoconstriction.⁸² Why some, but not all, athletes develop EIBw_A should be the main focus of research in this field in the future, and it is crucial that athletes with this specific endotype are separated from those with EIB_A in upcoming studies, because the underlying mechanisms of these conditions probably differs. Forthcoming research should head toward these hypotheses.

Genetic susceptibility to EIB is a possible cause that should be explored in the future. There are several genetic alterations that may predispose to or protect athletes from EIBw_A, of which some have already been pointed out and need further exploration: (i) the upregulation of PPT-1 gene, from which substance P is derived from, and the over-expression of NK-1 receptors⁸²; (ii) functional polymorphisms of the aqueous water channel aquaporin (Aqp) 5 that may contribute to protecting the airways reactivity to nonspecific stimulus⁷⁷; (iii) a tendency toward increased epithelial damage and susceptibility to oxidative stress.⁹³ Genetic alterations that account for intrinsic antioxidants and inflammatory mediators in bronchial tissue may indicate whether inhalant irritants will initiate the development of EIB. It has been claimed that acute physical exercise performed at high intensity may result in oxidative stress, due to reactive oxygen species being generated excessively by enhanced oxygen consumption. This phenomenon, usually defined as *exercise-induced oxidative*

stress, has been implicated in the damage of cellular membranes, increased cellular swelling, and decreased cell membrane fluidity. It is noteworthy that CC16 is produced to protect the respiratory tract against inflammation, but also against oxidative stress.⁷² Interestingly, CC16 gene polymorphism has been associated with BHR.⁹⁴ It has been recently evidenced that levels of 8-isoprostane in exhaled breath condensate increase after training in swimmers, suggesting that exercise-induced hyperpnoea in a chlorinated pool environment increases airways oxidative stress.⁹⁵ The evidence in a mouse model that BHR can be induced by a single hypochlorite-ovalbumin instillation, independently of bronchial influx of inflammatory cell, highlighted the role of transient receptor potential ankyrin 1 (TRPA1) channel on nociceptive airway sensory nerves in nonallergic BHR.⁸⁷ Question remains if a similar mechanism could occur in the athlete exposed to irritants such as disinfection by-products in swimming pool or ozone and others when training outdoor, independent of their atopic and asthmatic status.⁸² Currently, there is no published research relating genotype to EIB specifically in regard to swimmers and chloramine exposure and that is a pertinent hypothesis to pursue.

As mentioned, current views on the EIB pathogenesis go well beyond initial osmotic and thermal hypotheses. New cytokines are being investigated in the context of their potential contribution to exercise-associated respiratory symptoms.⁹⁶ A promising research field that remains unexplored pertains to cytokine imbalance in the pathogenesis of EIB. Studies are scarce regarding Th1/Th2 response in EIB-affected subjects.⁹⁷ Thus, there are still many open questions and further studies are needed with respect to various aspects of the pathogenesis of EIB.

Epithelial injury is induced upon repeated and sustained exposure of the airways to high volumes of air during intensive exercise. These effects are even stronger when exercise is performed in an irritant environment (chlorine for swimmers or cold air for winter sports). The Clara Cell secretory protein 16 is present at the luminal side of the epithelium and may diffuse to the blood vessels when the epithelium is damaged. As such, it can be used as a serum biomarker of airway epithelial injury. Activation or injury of the epithelium may cause release of damage-associated molecular patterns (DAMPs), such as uric acid or high mobility group box 1 (HMGB-1). These molecules can directly stimulate cells of the innate immune system (e.g. macrophages), with the induction of pro-inflammatory cytokines (TNF, IL-1 β , or IL-6). These cytokines are involved in differentiation of Th17 cells or type 3 innate lymphoid cells. Interleukin-17A (IL-17A) induces IL-8 production by the airway epithelial and structural cells, which is a well-known chemokine for neutrophils. On the other hand, irritants such as hypochlorite might also directly activate transient receptor potential channels A1 (TRPA1) on afferent nerves and cause release of substance P or neurokinin A. These neuromediators activate mast cells, which release histamine, prostaglandins, and leukotrienes (LT) such as Cys LT and LTB4 that might cause bronchoconstriction. Lastly, increased ventilation also leads to airway dehydration, increased airway osmolarity, and thereby cell shrinkage followed by mediator release and bronchoconstriction.

Despite the increased risk of EIB in elite sports, the physical, mental health, and lifestyle benefits of participation in the sport are numerous and with attention to the current findings and future research, healthy participation in sports at the elite level can be improved and enjoyed.

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CONFLICTS OF INTERESTS

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

MC conceived and designed the paper. MC and SS drafted the first complete version of the article and the entire reviewed version. SS was responsible for the figure. MK, AM, DB, KH, LD, and MK reviewed the manuscript for important intellectual content and added a valuable contribution by inputting their expertise in this specific field of knowledge. The article has more than five authors since it was proposed by the EAACI president to the Interest Group of Allergy, Asthma and Sports, but the contribution of experts in the area was considered essential for a valuable and accurate article. All authors approved the final version to be published.

REFERENCES

- Weiler JM, Bonini S, Coifman R, et al. American academy of allergy, asthma & immunology work group report: exercise-induced asthma. *J Allergy Clin Immunol*. 2007;119:1349-1358.
- Jones RS, Buston MH, Wharton MJ. The effect of exercise on ventilatory function in the child with asthma. *Br J Dis Chest*. 1962;56:78-86.
- Godfrey S. *Exercise Testing in Children*. London: WB Saunders; 1974.
- Bonini M, Palange P. Exercise-induced bronchoconstriction: new evidence in pathogenesis, diagnosis and treatment. *Asthma Res Pract*. 2015;1:2.
- Bonini S. EIB or not EIB? That is the question. *Med Sci Sports Exerc*. 2008;40:1565-1566.
- Parsons JP, Hallstrand TS, Mastronarde JG, et al. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med*. 2013;187:1016-1027.
- Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet*. 2006;368:804-813.
- Lund TK, Pedersen L, Anderson SD, Sverrild A, Backer V. Are asthma-like symptoms in elite athletes associated with classical features of asthma? *Br J Sports Med*. 2009;43:1131-1135.
- Haataela T, Malmberg P, Moreira A. Mechanisms of asthma in Olympic athletes – practical implications. *Allergy*. 2008;63:685-694.
- Couto M, Stang J, Horta L, et al. Two distinct phenotypes of asthma in elite athletes identified by latent class analysis. *J Asthma*. 2015;52:897-904.
- Fitch K. An overview of asthma and airway hyper-responsiveness in Olympic athletes. *Br J Sports Med*. 2012;46:413-416.
- Boulet LP, O'Byrne PM. Asthma and exercise-induced bronchoconstriction in athletes. *N Engl J Med*. 2015;372:641-648.

13. Bougault V, Turmel J, St-Laurent J, Bertrand M, Boulet L-P. Asthma, airway inflammation and epithelial damage in swimmers and cold-air athletes. *Eur Respir J*. 2009;33:740-746.
14. Bougault V, Loubaki L, Joubert P, et al. Airway remodeling and inflammation in competitive swimmers training in indoor chlorinated swimming pools. *J Allergy Clin Immunol*. 2012;129:351-358.
15. Seys SF, Hox V, Van Gerven L, et al. Damage-associated molecular pattern and innate cytokine release in the airways of competitive swimmers. *Allergy*. 2015;70:187-194.
16. Hull JH, Ansley L, Price OJ, Dickinson JW, Bonini M. Eucapnic voluntary hyperpnea: gold standard for diagnosing exercise-induced bronchoconstriction in athletes? *Sports Med*. 2016;46:1083-1093.
17. Price OJ, Ansley L, Hull JH. Diagnosing exercise-induced bronchoconstriction with eucapnic voluntary hyperpnea: is one test enough? *J Allergy Clin Immunol Pract*. 2015;3:243-249.
18. Price OJ, Ansley L, Levai IK, et al. Eucapnic voluntary hyperpnea testing in asymptomatic athletes. *Am J Respir Crit Care Med*. 2016;193:1178-1180.
19. Van der Eycken S, Schelpe A, Marijse G, et al. Feasibility to apply eucapnic voluntary hyperventilation in young elite athletes. *Respir Med*. 2016;111:91-93.
20. Pedersen L, Lund TK, Barnes PJ, Kharitonov SA, Backer V. Airway responsiveness and inflammation in adolescent elite swimmers. *J Allergy Clin Immunol*. 2008;122:322-327.
21. Del Giacco SR, Firinu D, Bjerner L, Carlsen KH. Exercise and asthma: an overview. *Eur Clin Respir J*. 2015;3:279-284.
22. Price OJ, Ansley L, Menzies-Gow A, Cullinan P, Hull JH. Airway dysfunction in elite athletes – an occupational lung disease? *Allergy*. 2013;68:1343-1352.
23. Rundell KW, Anderson SD, Sue-Chu M, Bougault V, Boulet LP. Air quality and temperature effects on exercise-induced bronchoconstriction. *Compr Physiol*. 2015;5:579.
24. Katelaris CH, Carrozzi FM, Burke TV, Byth K. A springtime olympics demands special consideration for allergic athletes. *J Allergy Clin Immunol*. 2000;106:260-266.
25. Sacha JJ, Quinn JM. The environment, the airway, and the athlete. *Ann Allergy Asthma Immunol*. 2011;106:81-87.
26. Helenius IJ, Tikkanen HO, Haahtela T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. *Br J Sports Med*. 1998;32:125-129.
27. Helenius IJ, Tikkanen HO, Sarna S, Haahtela T. Asthma and increased bronchial responsiveness in elite athletes: atopy and sport event as risk factors. *J Allergy Clin Immunol*. 1998;101:646-652.
28. Anderson SD, Kippelen P. Exercise-induced bronchoconstriction: pathogenesis. *Curr Allergy Asthma Rep*. 2005;5:116-122.
29. Bougault V, Turmel J, Boulet L-P. Bronchial challenges and respiratory symptoms in elite swimmers and winter sport athletes. *Chest*. 2010;138:31-37.
30. McFadden ERJ, Ingram RHJ. Exercise-induced asthma: observations on the initiating stimulus. *N Engl J Med*. 1979;301:763-769.
31. 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*. 1998;158:597-601.
32. Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax*. 2002;57:875-879.
33. Sue-Chu M, Karjalainen EM, Laitinen A, Larsson L, Laitinen LA, Bjerner L. Placebo-controlled study of inhaled budesonide on indices of airway inflammation in bronchoalveolar lavage fluid and bronchial biopsies in cross-country skiers. *Respiration*. 2000;64:417-425.
34. Moreira A, Delgado L, Palmares C, et al. Competitive swimmers with allergic asthma show a mixed type of airway inflammation. *Eur Respir J*. 2008;31:1139-1141.
35. Bonsignore MR, Morici G, Vignola AM, et al. Increased airway inflammatory cells in endurance athletes: what do they mean? *Clin Exp Allergy*. 2003;33:14-21.
36. Mountjoy M, Fitch K, Boulet LP, Bougault V, van Mechelen W, Verhagen E. Prevalence and characteristics of asthma in the aquatic disciplines. *J Allergy Clin Immunol*. 2015;136:588-594.
37. Rundell KW, Sue-Chu M. Air quality and exercise-induced bronchoconstriction in elite athletes. *Immunol Allergy Clin North Am*. 2013;33:409-421.
38. Rundell KW. High levels of airborne ultrafine and fine particulate matter in indoor ice arenas. *Inhal Toxicol*. 2003;15:237-250.
39. Lumme A, Haahtela T, Ounap J, et al. Airway inflammation, bronchial hyperresponsiveness and asthma in elite ice hockey players. *Eur Respir J*. 2003;22:113-117.
40. Rundell KW. Pulmonary function decay in women ice hockey players: is there a relationship to ice rink air quality? *Inhal Toxicol*. 2004;16:3.
41. Wilber RL, Rundell KW, Szmedra L, Jenkinson DM, Im J, Drake SD. Incidence of exercise-induced bronchospasm in Olympic winter sport athletes. *Med Sci Sports Exerc*. 2000;32:732-737.
42. Rundell KW, Caviston R, Hollenbach AM, Murphy K. Vehicular air pollution, playgrounds, and youth athletic fields. *Inhal Toxicol*. 2006;18:541-547.
43. Godfrey S. Exercise-induced asthma. In: Clark TJH, Godfrey S, eds. *Asthma*. London: Chapman and Hall; 1977: 57-58.
44. Larsson J, Anderson SD, Dahlén SE, Dahlén B. Refractoriness to exercise challenge: a review of the mechanisms old and new. *Immunol Allergy Clin North Am*. 2013;33:329-345.
45. Hallstrand TS, Moody MW, Aitken ML, Henderson WRJ. Airway immunopathology of asthma with exercise-induced bronchoconstriction. *J Allergy Clin Immunol*. 2005;116:586-593.
46. Hallstrand TS, Moody MW, Wurfel MM, Schwartz LB, Henderson WRJ, Aitken ML. Inflammatory basis of exercise-induced bronchoconstriction. *Am J Respir Crit Care Med*. 2005;172:679-686.
47. Daviskas E, Gonda I, Anderson SD. Local airway heat and water vapour losses. *Respir Physiol*. 1991;84:115-132.
48. Barnes PJ. Cholinergic control of airway smooth muscle. *Am Rev Respir Dis*. 1987;136:S42-S45.
49. McFadden ERJ, Gilbert IA. Exercise-induced asthma. *N Engl J Med*. 1994;330:1362-1366.
50. Helenius IJ, Ryttilä P, Metso T, Haahtela T, Venge P, Tikkanen HO. Respiratory symptoms, bronchial responsiveness, and cellular characteristics of induced sputum in elite swimmers. *Allergy*. 1998;53:346-352.
51. Sue-Chu M, Larsson L, Moen T, Rennard SI, Bjerner L. Bronchoscopy and bronchoalveolar lavage findings in cross-country skiers with and without "ski asthma". *Eur Respir J*. 1999;13:626-632.
52. Karjalainen EM, Laitinen A, Sue-Chu M, Altraja A, Bjerner L, Laitinen LA. Evidence of airway inflammation and remodeling in ski athletes with and without bronchial hyperresponsiveness to methacholine. *Am J Respir Crit Care Med*. 2000;161:2086-2091.
53. Helenius I, Haahtela T. Allergy and asthma in elite summer sport athletes. *J Allergy Clin Immunol*. 2000;106:444-452.
54. Helenius I, Ryttilä P, Sarna S, et al. Effect of continuing or finishing high-level sports on airway inflammation, bronchial hyperresponsiveness, and asthma: a 5-year prospective follow-up study of 42 highly trained swimmers. *J Allergy Clin Immunol*. 2002;109:962-968.
55. Vergès S, Devouassoux G, Flore P, et al. Bronchial hyperresponsiveness, airway inflammation, and airflow limitation in endurance athletes. *Chest*. 2005;127:1935-1941.
56. Schwartz LB, Delgado L, Craig T, et al. Exercise-induced hypersensitivity syndromes in recreational and competitive athletes: a PRAC-TALL consensus report (what the general practitioner should know about sports and allergy). *Allergy*. 2008;63:953-961.
57. Helenius I, Lumme A, Ounap J, et al. No effect of montelukast on asthma-like symptoms in elite ice hockey players. *Allergy*. 2004;59:39-44.

58. Hoshino Y, Koya T, Kagamu H, et al. Effect of inhaled corticosteroids on bronchial asthma in Japanese athletes. *Allergol Int*. 2015;64:145-149.
59. Carlsen K-H, Anderson S, 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*. 2008;63:387-403.
60. Moreira A, Palmares C, Lopes C, Delgado L. Airway vascular damage in elite swimmers. *Respir Med*. 2011;105:1761-1765.
61. Couto M, Andrade P, Pereira M, et al. Effect of competitive swimming on airway inflammation: a 3-yr longitudinal study. *Pediatr Allergy Immunol*. 2014;25:193-195.
62. Chimenti L, Morici G, Paternò A, et al. Bronchial epithelial damage after a half-marathon in nonasthmatic amateur runners. *Am J Physiol Lung Cell Mol Physiol*. 2010;298:L857-L862.
63. Chimenti L, Morici G, Paternò A, et al. Endurance training damages small airway epithelium in mice. *Am J Respir Crit Care Med*. 2007;175:442-449.
64. Anderson SD, Kippelen P. Airway injury as a mechanism for exercise-induced bronchoconstriction in elite athletes. *J Allergy Clin Immunol*. 2008;122:225-235.
65. Bolger C, Tufvesson E, Anderson SD, et al. Effect of inspired air conditions on exercise-induced bronchoconstriction and urinary CC16 levels in athletes. *J Appl Physiol*. 2011;111:1059-1065.
66. Romberg K, Bjermer L, Tufvesson E. Exercise but not mannitol provocation increases urinary Clara cell protein (CC16) in elite swimmers. *Respir Med*. 2011;105:31-36.
67. Carbone S, Francaux M, Doyle I, et al. Changes in serum pneumoproteins caused by short-term exposures to nitrogen trichloride in indoor chlorinated swimming pools. *Biomarkers*. 2002;7:464-478.
68. Bolger C, Tufvesson E, Sue-Chu M, et al. Hyperpnea-induced bronchoconstriction and urinary CC16 levels in athletes. *Med Sci Sports Exerc*. 2011;43:1207-1213.
69. Kippelen P, Tufvesson E, Ali L, Bjermer L, Anderson SD. Urinary CC16 after challenge with dry air hyperpnea and mannitol in recreational summer athletes. *Respir Med*. 2013;107:1837-1844.
70. Kurowski M, Jurczyk J, Jarzębska M, et al. Association of serum Clara cell protein CC16 with respiratory infections and immune response to respiratory pathogens in elite athletes. *Respir Res*. 2014;15:45.
71. Seys SF, Feyen L, Keirsbilck S, Adams E, Dupont LJ, Nemery B. An outbreak of swimming-pool related respiratory symptoms: an elusive source of trichloramine in a municipal indoor swimming pool. *Int J Hyg Environ Health*. 2015;218:386-391.
72. Broeckeaert F, Bernard A. Clara cell secretory protein (CC16): characteristics and perspectives as lung peripheral biomarker. *Clin Exp Allergy*. 2000;30:469-475.
73. Carter JB, Banister EW, Blaber AP. Effect of endurance exercise on autonomic control of heart rate. *Sports Med*. 2003;33:33-46.
74. Filipe JA, Falcão-Reis F, Castro-Correia J, Barros H. Assessment of autonomic function in high level athletes by pupillometry. *Auton Neurosci*. 2003;104:66-72.
75. Kaltsatou A, Kouidi E, Fotiou D, Deligiannis P. The use of pupillometry in the assessment of cardiac autonomic function in elite different type trained athletes. *Eur J Appl Physiol Occup Physiol*. 2011;111:2079-2087.
76. Knöpfli BH, Bar-Or O. Vagal activity and airway response to ipratropium bromide before and after exercise in ambient and cold conditions in healthy cross-country runners. *Clin J Sport Med*. 1999;9:170-176.
77. Park C, Stafford C, Lockette W. Exercise-induced asthma may be associated with diminished sweat secretion rates in humans. *Chest*. 2008;134:552-558.
78. Goldsmith RL, Bigger JT Jr, Bloomfield DM, Steinman RC. Physical fitness as a determinant of vagal modulation. *Med Sci Sports Exerc*. 1997;29:812-817.
79. Couto M, Silva D, Santos P, Queirós S, Delgado L, Moreira A. Exploratory study comparing dysautonomia between asthmatic and non-asthmatic elite swimmers. *Rev Port Pneumol*. 2015;21:22-29.
80. Langdeau JB, Turcotte H, Bowie DM, Jobin J, Desgagné P, Boulet LP. Airway hyperresponsiveness in elite athletes. *Am J Respir Crit Care Med*. 2000;161:1479-1484.
81. Stang J, Stensrud T, Mowinckel P, Carlsen KH. Parasympathetic activity and bronchial hyperresponsiveness in athletes. *Med Sci Sports Exerc*. 2016;48:2100-2107.
82. Moreira A, Delgado L, Carlsen KH. Exercise-induced asthma: why is it so frequent in Olympic athletes? *Expert Rev Respir Med*. 2011;5:1-3.
83. 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*. 1996;16:73-82.
84. Crimi N, Palermo F, Oliveri R, et al. Influence of antihistamine (astemizole) and anticholinergic drugs (ipratropium bromide) on bronchoconstriction induced by substance P. *Ann Allergy Asthma Immunol*. 1990;65:115-120.
85. Wessler I, Kirkpatrick CJ. Acetylcholine beyond neurons: the non-neuronal cholinergic system in humans. *Br J Pharmacol*. 2008;154:1558-1571.
86. Bonini M, Fioretti D, Sargentini V, et al. Increased nerve growth factor serum levels in top athletes. *Clin J Sport Med*. 2013;23:228-231.
87. Hox V, Vanoirbeek JA, Alpizar YA, et al. Crucial role of transient receptor potential ankyrin 1 and mast cells in induction of nonallergic airway hyperreactivity in mice. *Am J Respir Crit Care Med*. 2013;187:486-493.
88. Stensrud T, Mykland KV, Gabrielsen K, Carlsen KH. Bronchial hyperresponsiveness in skiers: field test versus methacholine provocation? *Med Sci Sports Exerc*. 2007;39:1681-1686.
89. Bougault V, Boulet LP. Airway dysfunction in swimmers. *Br J Sports Med*. 2012;46:402-406.
90. Fitch KD. Beta2-agonists at the olympic games. *Clin Rev Allergy Immunol*. 2006;31:259-268.
91. Knöpfli BH, Luke-Zeitoun M, von Duvillard SP, Burki A, Bachlechner C, Keller H. High incidence of exercise-induced bronchoconstriction in triathletes of the Swiss national team. *Br J Sports Med*. 2007;41:486-491.
92. Bougault V, Turmel J, Boulet LP. Airway hyperresponsiveness in elite swimmers: is it a transient phenomenon? *J Allergy Clin Immunol*. 2011;127:892-898.
93. Bucchieri F, Puddicombe SM, Lordan JL, et al. Asthmatic bronchial epithelium is more susceptible to oxidant-induced apoptosis. *Am J Respir Cell Mol Biol*. 2002;27:179-185.
94. Sengler C, Heinzmann A, Jerkic SP, et al. Clara cell protein 16 (CC16) gene polymorphism influences the degree of airway responsiveness in asthmatic children. *J Allergy Clin Immunol*. 2003;111:515-519.
95. Morissette MC, Murray N, Turmel J, Milot J, Boulet LP, Bougault V. Increased exhaled breath condensate 8-isoprostane after a swimming session in competitive swimmers. *Eur J Sport Sci*. 2016;16:5.
96. Kuchar E, Miskiewicz K, Nitsch-Osuch A, Kurpas D, Han S, Szenborn L. Immunopathology of exercise-induced bronchoconstriction in athletes – a new modified inflammatory hypothesis. *Respir Physiol Neurobiol*. 2013;187:82-87.
97. Bonini M, Gramiccioni C, Fioretti D, et al. Asthma, allergy and the Olympics: a 12-year survey in elite athletes. *Curr Opin Allergy Clin Immunol*. 2015;15:184-192.

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