Article:
Ameri, S., Stang, J., Walsted, E. et al. (1 more author) (2025) Mechanisms and Biomarkers of Exercise-induced Bronchoconstriction: Current Insights and Future Directions. Immunology and Allergy Clinics of North America, 45 (1). pp. 63-75. ISSN 0889-8561

https://doi.org/10.1016/j.iac.2024.08.009

Mechanisms and Biomarkers of Exercise-Induced Broncho-constriction: Current Insights and Future Directions

Immunology and Allergy Clinics of North America

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Key Points

- Exercise-induced bronchoconstriction (EIB) is common in athletes and individuals with pre-existing asthma – each potentially having distinct features and underlying mechanisms.

- High ventilatory load and subsequent alterations in airway physiology during vigorous exercise are major contributing factors in the development of EIB.

- Inhalation of increased volumes of unconditioned dry cold air is considered the primary stimulus leading to EIB due to airway dehydration, epithelial injury, mast cell activation, inflammatory mediator release and neuronal activation.

- Epithelial injury is thought to be central in the development and progression of EIB in athletes, and it appears that this process is reversible with reduced training load / exercise cessation.

- Identification of EIB biomarkers provides valuable insight concerning underlying mechanisms and permits the development of future diagnostic methods and treatment strategies.

Keywords: EIB, mast cells, biomarker, asthma, athlete, airway injury.

Clinics Care Points

- Utilizing biomarkers in conjunction with bronchial provocation tests elucidates underpinning mechanisms concerning the development and progression of EIB.

- Understanding pathophysiological mechanisms in the context of EIB is important to permit targeted treatment strategies.

- EIB phenotyping according to inflammatory sub-types and clinical characteristics such as age of onset and disease severity supports personalized care.

Synopsis

Exercise-induced bronchoconstriction (EIB) refers to temporary lower airway narrowing that occurs during or after vigorous physical exertion, with a high incidence in athletes and individuals with pre-existing asthma. The pathophysiology of EIB is not completely understood, but it is thought to involve a complex interplay between airway epithelial changes, immune responses, and environmental interactions. Phenotypic differences are apparent among those affected by EIB, which may influence susceptibility and manifestation, highlighting the necessity for future studies to characterize well-defined subgroups. This clinical review aims to summarize the complex mechanisms underlying EIB, explore the role of biomarkers in the diagnosis and management, and identify current gaps in knowledge to pave the way for future scientific discoveries.

1. Introduction

Exercise-induced bronchoconstriction (EIB) is a condition characterized by transient lower airway narrowing that occurs during and after vigorous physical exertion, with a high incidence in athletes (1) and individuals with pre-existing asthma (2). The incidence of EIB across different populations indicates phenotypic variability. The etiology of EIB is multifactorial, precipitated by ventilatory demands during high-intensity exercise leading to inhalation of noxious particles, pollutants, aeroallergens, and unconditioned cold dry air. This clinical review delves into both traditional etiological theories of EIB and more recent explanatory models, while exploring the role of biomarkers in diagnosis and management.

1.1. Airway Demands During Intense Exercise

Vigorous exercise places significant stress on the respiratory system (3). During high-intensity exercise, minute ventilation (V_E) can surge to over 200 litres in elite or highly trained athletes (4). Ventilation rates in excess of 30 litres per minute, result in a shift in breathing pattern from primarily nasal to oronasal airflow (5). This leads to the inhalation of air that is neither humidified or filtered by the nasal passages, exposing the lower airways to cold and dry air alongside increased levels of aeroallergens, noxious particles, and pollutants (6). Thus, with higher breathing rates, the lower respiratory tract adopts the critical role of adjusting the temperature and moisture of inspired air. This exposure causes moisture to evaporate from the airway surface lining and contributes to mechanical airway stress (7,8).

1.2 Revisiting Classical Theories of EIB

Historically, the term exercise-induced asthma was used to describe bronchoconstriction associated with exercise. However, it subsequently became apparent that exercise induces bronchoconstriction in some individuals without asthma, leading to the more inclusive and specific term EIB. This distinction is important as it acknowledges that exercise can be a direct trigger for bronchoconstriction independent of a clinical asthma diagnosis.

Initially, two main theories were proposed to describe the mechanisms of EIB in people with asthma. First, *the thermal theory,* proposed by McFadden and colleagues in the mid 1980's, hypothesized that airway cooling, followed by rapid rewarming upon exercise cessation triggers a reactive hyperaemic vascular response (9) – involving capillary leakage and airway wall oedema, leading to mucosal thickening and airway narrowing (10). Anderson and colleagues subsequently observed that neither airway cooling nor rewarming is necessary for EIB to occur, leading to *the osmotic* or *airway-drying theory* (11). The *osmotic theory* suggests that water loss within intra-thoracic airways creates a hyperosmotic environment, prompting the release of bronchoconstrictive agents (12). Specifically, moisture loss extends distally, causing dehydration of the small airways and a transient increase in airway surface liquid osmolarity. Resident cells in the distal airways, such as mast cells, respond to changes in osmolarity, resulting in the release of pro-inflammatory mediators (e.g. histamine, leukotrienes, and prostaglandins). In turn, these mediators induce airway smooth muscle contraction leading to bronchoconstriction in susceptible individuals. Anderson and colleagues later suggested that the thermal and osmotic theories could occur in unison given inspiration of cold air not only cools the airways but also increases the numbers of airway generations becoming dehydrated in the humidifying process (11).

1.3 EIBa versus EIBwa

EIB with asthma (EIBa) describes the occurrence of bronchial obstruction during or after exercise in asthmatic patients. In contrast, EIB without asthma (EIBwa), refers to bronchial obstruction in those without other signs and symptoms of clinical asthma (13). In people with

asthma, EIB is a common manifestation, where exercise triggers asthma symptoms (e.g., cough, wheeze, and dyspnea) due to underlying airways hyperresponsiveness (AHR) and airway inflammation. Individuals with EIBa also experience asthma symptoms outside the setting of exercise. It is thought that asthmatic airways are more susceptible to environmental triggers due to chronic underlying inflammation. Other common asthma triggers include allergens (e.g., pollen and pet dander), respiratory infections (most often viral) and airborne irritants (e.g., smoke and pollution) (14,15). It is important to note that asthma is a highly heterogeneous condition with distinct patterns of inflammation reflecting diverse clinical presentation and underlying mechanisms (16). Specifically, type-2 high asthma is characterised by raised eosinophilic inflammation, whereas type-2 low asthma includes neutrophilic and paucigranulocytic asthma. Mixed granulocytic asthma is characterised by the co-existence of eosinophilic and neutrophilic inflammation (17). Phenotyping by inflammatory patterns therefore helps to tailor treatment according to specific characteristics such as triggers, age of onset, and disease severity (16,18).

In the context of EIBwa, symptoms typically only occur when engaging in intense exercise (19). However, rather than the traditional type 2-high asthma phenotype, individuals with EIBwa (particularly athletes participating in aquatic and winter-based sports) often develop non-atopic (type 2-low) phenotype (otherwise referred to as ‘sport asthma’) (20). In this scenario, symptoms may only occur in particular environments, such as ice rinks, cold climates, or indoor swimming pools (21).

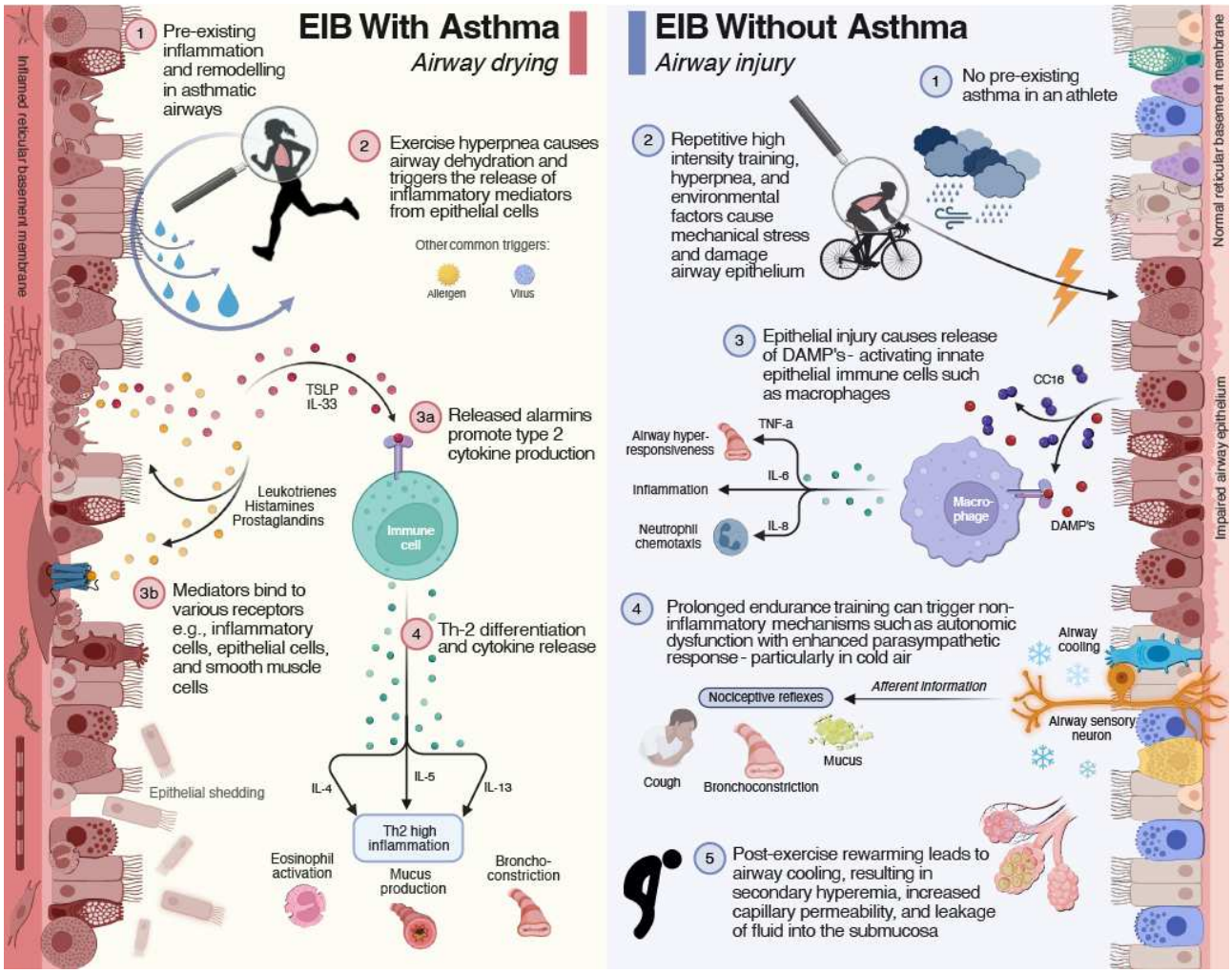

Figure 1: Potential Mechanisms of EIB With and Without Asthma. **Left** – in EIB with asthma, exercise triggers bronchoconstriction. Increased airway inflammation due to bronchial hyperresponsiveness, mainly through type 2 inflammatory mediators. The asthmatic airway epithelium with airway remodeling involving structural changes such as increased deposition of proteins, hypertrophy of smooth muscle cells, mucus hypersecretion, and thickening of the reticular basement membrane due to deposition of extracellular matrix proteins (i.e., collagen and elastin). **Right –** endurance athlete undertaking regular exercise (i.e., chronic exercise hyperpnea) causing injury to the airway epithelium. Injury-repair process induces the release of damage-associated molecular patterns (DAMP's), which activate epithelial cells and produce an inflammatory response. Other potential mechanisms include autonomous nerve involvement and post-exercise hyperemia. Created with BioRender.com.

2. Proposed Mechanisms of EIB

The precise mechanisms that trigger EIB remain to be fully understood; however, several factors are likely involved including, but not limited to, mast cell activation, inflammatory mediators, epithelial injury, and autonomous nerve activation. The following sections will provide a detailed overview of the proposed mechanisms of EIB.

2.1 Mast Cells and Eicosanoids

Water loss from airway epithelium, induced by high ventilatory demand during exercise, leads to a local increase in osmolarity, which, in turn, triggers the release of inflammatory mediators from activated epithelial residing cells, including mast cells (22). Mast cells release histamines and eicosanoids such as cysteinyl leukotrienes (CysLTs) and prostaglandins (PG) (23), which cause smooth muscle contraction and airway narrowing (11) (Figure 1). Mast cells and inflammatory mediators play a central role in EIB. It has been shown that the density of tryptase- and CPA3-positive mast cells per volume is significantly higher in individuals with EIBa compared to people with EIBwa and healthy controls (24). Further, the severity of EIB measured by the maximum fall in FEV_1 exercise is associated with the density of mast cells relative to the epithelial volume (24). Individuals with EIBa also have a greater degree of mast cell activation assessed by high levels of histamine, tryptase, and CysLTs in induced sputum post-exercise (25), and in urine samples after mannitol inhalation (22).

In a recent study examining the contractile prostanoid component of EIB, hyperosmolar mannitol induced bronchial contraction was inhibited in an ex vivo model, by eliminating mast cells (26). Hyperosmolar induced bronchoconstriction was also prevented by combining receptor antagonists of $CysLT_1$, histamine (H_1) and thromboxane (TP) (26). However, solely inhibiting CysLTs did not entirely prevent EIB, indicating the involvement of additional bronchoconstrictive eicosanoids and/or a decrease in bronchoprotective mediators such as prostaglandin E_2 (PGE_2) (26,27).

The significance of eicosanoids in EIBa is supported in a study comparing induced sputum and bronchoalveolar lavage (BAL) fluid obtained before and after an exercise challenge test in asthmatic subjects with and without EIB (28). The study found that EIBa subjects tended to have higher baseline levels of CysLTs in comparison with asthmatic subjects without EIB. Furthermore, higher basal sputum levels of CysLTs and prostaglandin D_2 (PGD_2) were associated with AHR and both the post-exercise and absolute change in CysLTs and PGD_2 levels were associated with EIB severity. Individuals with more severe EIB also had lower methacholine PC_{20} levels (the provocative concentration of methacholine that results in a 20% fall in FEV_1). Secreted phospholipase A_2 group 10 ($sPLA_2$-X) has also been shown to be associated with AHR, which could explain the elevated basal levels of phospholipid turnover and eicosanoid synthesis observed in people with EIBa (28).

A protective role of some eicosanoids, such as PGE_2, has been suggested (29). Inhaled mannitol induces mast cell degranulation and activated mitogen-activated protein kinase (MAPK) pathways, thereby causing de novo eicosanoid and cytokine synthesis, and the addition of PGE_2 significantly reduced mannitol-induced degranulation through prostaglandin EP_2 and prostaglandin EP_4 receptors (30). These findings are particularly interesting given the ratio of CysLTs to PGE_2 is increased in the induced sputum of patients with EIBa (31). It has been suggested that protective substances (e.g., PGE_2) may explain the refractory period observed after exercise (32).

2.2 Airway Inflammatory Milieu and Exercise

Airway inflammation and structural remodeling in asthma is well-described (14,16,33). In type 2-high asthma, certain stimuli can induce the airway epithelium to react with a broad inflammatory response involving interleukins (IL) such as IL-4, IL-5, and IL-13, leading to typical asthma signs and symptoms; e.g., eosinophilia mucus production, and bronchospasm (34). This response is initiated by the release of alarmins such as thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 from the airway epithelium after exposure to various triggers such as allergens, viruses, and exercise (35). Multiple studies have shown that type-2 high related inflammatory parameters such as fractional exhaled nitric oxide (FeNO), leukotrienes and eosinophils are increased in people with EIBa compared to healthy controls and people with asthma without EIB, and it seems that these inflammatory parameters are correlated with EIB severity (31,36,37). Moreover, it has been shown that airway epithelial cells in EIBa have a greater release of alarmins TSLP and IL-33 in response to epithelial

mechanical wounding and osmotic stress compared to people with asthma without EIB and healthy controls (24). Collectively, these findings suggest that people with type 2-high asthma are at heightened susceptibility to EIBa.

To date, the studies that have examined airway inflammation in people with EIBwa show conflicting results, partly due to differences in methodology and study population. In studies conducted during the late 1990s, researchers performed bronchoscopy and BAL examinations on cross-country skiers with and without "ski asthma" (38). The authors found that cross-country skiers had minor to moderate degree of macroscopic inflammation in the proximal airways at bronchoscopy and a BAL fluid profile that had a higher inflammatory index. In a similar study it was found that competitive skiers without asthma had higher neutrophil counts in bronchial biopsy specimens compared to subjects with mild asthma and healthy controls (39). Specifically, T-lymphocyte, macrophage, and eosinophil counts were significantly higher in elite skiers and asthmatic subjects compared to healthy controls. In skiers, neutrophil counts were more than two-fold greater in comparison to asthmatic subjects (39).

Other studies show minimal to no airway inflammation measured as neutrophil and eosinophil counts in induced sputum of both swimmers and cold-air athletes as compared to healthy or asthmatic non-athletes (40–42). Airway dysfunction and inflammation has previously been evaluated in symptomatic pool- and non-pool-based athletes (43). All experienced EIB symptoms and were not treated with steroids prior to the study. It was found that

pool-based athletes exhibited better lung function (FEV_1) at baseline but had greater AHR compared to non-pool-based athletes (measured as percent pre-to-post reduction in FEV_1). Although more pool-based athletes had EIB, there was no difference in eosinophilic airway inflammation between the two groups. However, sputum induction indicated that athletes with EIB had higher levels of eosinophils and epithelial cells (43). Elevated FeNO and polymorphonuclear neutrophils (PMNs) have also previously been reported in the sputum of healthy runners, in comparison to inactive controls (44). This further supports the concept that exercise can trigger the release of pro-inflammatory compounds.

In an extensive review examining airway inflammation and oxidative imbalances induced by exercise in people without asthma mainly focusing on exhaled breath condensate (EBC), it was reported that granulocyte cellularity increases predominantly in cases of acute, prolonged high-intensity exercise (45). It was also observed that extended acute moderate exercise (>60 min) leads to an elevation in pulmonary inflammatory mediators such as IL-8, LTB_4, and LTE_4. After more than thirty minutes of exercise, a systematic increase in prooxidants is observed, and exercising at high altitudes leads to an increase in lung lipid peroxidation. Whilst there are limited studies evaluating the impact of chronic exercise, there appears to be a tendency towards an increase in cellularity indicative of chronic airway inflammation particularly those exposed to cold air and chlorine (45).

Murphy and colleagues examined gene expression in epithelial brushings from individuals with EIBa and EIBwa and identified 120 differentially expressed genes (DEGs), thus highlighting roles for IL-33, IL-18, and IFN-γ-related signaling pathways (46). These DEGs were correlated with markers of airway physiology and inflammation. Additionally, interactions between airway epithelial cells (AECs), mast cells (MCs) and eosinophils (EOS) were explored, revealing AECs' potential to sustain type 2 inflammation in MCs and enhance IL-33-induced gene expression, while EOS upregulated IFNG and IL-13 expression in response to various stimuli (46).

2.3 Airway Injury and Integrity

The airway epithelium acts as the first line of defense against the external environment encountered by the upper and lower airways. It forms a tightly controlled barrier, effectively blocking the entry of inhaled allergens, pathogens, pollutants, and various toxic agents into the deeper lung spaces. Exercise, especially at high intensity or in extreme conditions such as cold, dry, or polluted air, appears to cause damage to the airway epithelium (8). In the context of elite athletes, dehydration and increased mechanical stress to the airway surface due to severe exercise hyperpnea are considered to be important causative factors contributing to the development and progression of EIB due to an injury-repair process (8).

It is recognized that damage-associated molecular patterns (DAMPs) are secreted from epithelial cells due to tissue damage, triggering activation of airway innate immune cells like macrophages, leading to production of proinflammatory cytokines including TNF-α, IL-6, IL-8, IL-1β, and IL-1α (47) (Figure 1). Most studies have relied on surrogate markers such as club/clara cell secreted protein (CC16), which only indirectly indicates epithelial damage, and the use and clinical significance of these markers remain largely inadequately examined and validated (48).

Despite this, previous studies have shown that continuous exercise (i.e., sustained exercise hyperpnea) leads to increased levels of circulating CC16 protein, while intermittent exercise does not elicit the same effect (49). One of the few studies examining epithelial structure and function utilized endobronchial biopsies in young elite competitive cross-country skiers without asthma and compared to patients with mild asthma and healthy controls (39). This study reported that 75% of skiers without an asthma diagnosis had evidence of AHR to methacholine. Tenascin expression, an extracellular matrix protein, in endobronchial biopsy specimens (measured via the thickness of the tenascin-specific immunoreactivity band in the basement membrane) was increased in elite skiers and asthma sub-groups compared to healthy controls (39).

It is important to note that, there also appears to be evidence of epithelial injury in EIBa. In a previous study examining the concentration of columnar epithelial cells in induced sputum

in people with asthma without EIB, epithelial shedding was significantly higher in EIBa despite no difference in lung function, symptoms, or response to bronchodilator treatment (25,31).

A study examining the effects of exercise cessation found that individuals who ceased high-level swimming training, bronchial hyperresponsiveness and asthma showed signs of attenuation or complete resolution (50). Conversely, mild eosinophilic airway inflammation intensified among highly trained swimmers who continued their active regimen over the course of a 5-year follow-up period. These findings imply a partial reversibility of EIB, indicating its potential development during and subsequent resolution after an active athletic career (50).

2.4 Autonomic Nervous System Activity in EIB

The high prevalence of EIBwa in athletes has prompted theories of alternative non-inflammatory mechanisms such as autonomic dysfunction with an enhanced parasympathetic response induced by prolonged physical endurance training. The autonomic nervous system plays an important role in regulating airway caliber and exposure to cold air is shown to cause parasympathetic stimulation of airways, contributing to EIB (51). Endurance athletes demonstrate heightened parasympathetic activity, as evidenced by heart rate variability (HRV) (52) and pupillometry (53,54), with correlations to maximal oxygen uptake (VO_{2max}) (55). Interestingly, increased parasympathetic activity is found in athletes and non-athletes

with AHR with significant associations to methacholine sensitivity (52,56–58). Indeed, the high prevalence of AHR to methacholine reported in athletes, may reflect an increased parasympathetic bronchial activity as methacholine is a synthetic choline ester that acts as a non-selective muscarinic receptor agonist in the parasympathetic nervous system. Furthermore, Knopfli and co-workers have previously identified a relationship between EIB, the reversibility to inhaled ipratropium bromide (an anti-cholinergic bronchodilator), and parasympathetic activity measured by HRV, both in athletes (59) and children (60). This suggests that the parasympathetic nervous system contributes to the pathogenesis of EIB in endurance trained individuals.

2.4 Neurogenic Inflammation and Genetic Susceptibility

A dysfunctional neuroendocrine–immune interface may 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. Increased circulating levels of substance P, one of the major initiators of neurogenic inflammation, have been found after strenuous exercise (61). Animal models have supported these findings, but only few studies have evaluated this in humans (62). Genetic susceptibility to EIB has been associated with the gene for the aqueous water channel aquaporin 5 in mice (63). Airway hydration during exercise is mainly dependent on the water movement, following the osmotic force generated by sodium and chloride, through aquaporin channels expressed within the apical membrane of epithelial cells.

3. EIB Biomarkers

The diagnosis of EIB is clinically challenging due to the poor predictive value of respiratory symptoms and broad differential diagnosis. In those with normal resting lung function and negative bronchodilator responsiveness test, a form of indirect bronchial provocation (i.e., exercise testing, eucapnic voluntary hyperpnoea [EVH] or inhaled mannitol) is currently recommended to secure a diagnosis (65). In conjunction with bronchial provocation, biomarkers stand at the forefront of EIB diagnosis and management, offering insights into the mechanisms of airway inflammation and injury.

3.1 Exhaled biomarkers

FeNO is a non-invasive indirect biomarker of type 2 airway inflammation (activation of IL-4 / IL-13 pathway), that has an established role in the assessment and management of asthma (66). FeNO is elevated in many people with asthma and can be increased in some individuals with EIB (67). FeNO measures the concentration of nitric oxide (NO) in exhaled breath. The measurement of FeNO is a relatively accessible and simple method to quantify type 2 inflammation. NO is present in exhaled breath due to nitric oxide synthase upregulation that occurs when eosinophils infiltrate the airways. While FeNO may not be specific for diagnosing EIB, it can help identify underlying eosinophilic airway inflammation and guide anti-inflammatory treatment. A recent large retrospective analysis found that an elevated FeNO

(≥25 ppb) is a poor predictor of EIB in athletes (68) – whereas raised FeNO (≥40 ppb) provides good specificity but has poor sensitivity. Due to the poor sensitivity and poor predictive values, a high FeNO should not be used in isolation or as a replacement for an indirect bronchial provocation challenge to secure a diagnosis of EIB (68).

Exhaled breath temperature and analyzing exhaled breath condensate (EBC) for pH, inflammatory mediators (e.g., prostaglandins, leukotrienes), and markers of oxidative stress have been proposed as non-invasive approach to evaluate airway inflammation and oxidative stress associated with EIB. It has previously been shown when comparing EIBa and healthy controls, that EBC pH is significantly reduced during exercise in people with EIBa (69). In addition, changes in EBC pH are related to the degree of bronchospasm in EIBa (69). It has also been shown that the concentration of Cys-LTs in EBC are higher in children with EIBa compared to healthy controls and asthmatic children without EIB, and these findings correlate with the decrease in FEV_1 post exercise (70). Other markers of inflammation in EBC have been found to be elevated in people with EIBa compared to healthy controls and people with asthma without EIB, such as eotaxin (71), endothelin-1 (72), lipoxin A4 (73). In contrast, anti-inflammatory markers such as annexin A5, has been found to be significantly lower in children with EIBa, compared to children with asthma without EIB (73).

3.2 Sputum Induction and Peripheral Biomarkers

Sputum analysis in people with EIB may be useful in examining airway inflammation and injury. In people with EIBa, the concentration of columnar epithelial cells in induced sputum is often increased (31). The presence of eosinophils in induced sputum has been used as a marker of airway inflammation in people with type 2-high asthma and might be increased in some patients with EIB, suggesting an eosinophilic inflammation component. Other markers of airway inflammation in sputum such a neutrophil count, histamine, eicosanoids, and DAMPs, offer a window into the inflammatory and cellular dynamics involved with EIB, but have yet to be investigated in detail. Peripheral eosinophil counts and bronchial biopsies provide histological insights into inflammatory mechanisms underpinning EIB, enabling targeted therapeutic interventions. Serum levels of periostin, which is induced by IL-13, is significantly greater in children with EIBa compared to asthmatic children with negative exercise and mannitol provocation tests, and also greater than in healthy controls (74). Urinary biomarkers, such as CC16 and levels leukotrienes, which may reflect airway inflammation and injury, have been suggested as potentially relevant biomarkers in EIB (75–77).

4. Future Perspectives and Unmet Needs

Despite recent advances concerning the underpinning mechanisms of EIB, several areas remain uncharted. As this review highlights, a logical extension for future studies is to clearly define and characterize sub-groups according to patterns of airway inflammation defined according to the predominant granulocyte (i.e., type-2 high vs. type 2-low inflammation). EIB severity, biological sex, exercise mode and intensity, athletic standard, environmental triggers and parasympathetic activity are also important considerations in the design of future

studies. This approach will shed light on the underpinning mechanisms associated with EIBa and EIBwa – and will help to better understand why some individuals (with and without asthma) appear to be more susceptible to EIB.

Epithelial injury as a consequence of sustained exercise hypernea and environmental exposure is a relatively unexplored area of research as it presents a significant challenge due to the requirement for precise assessment via invasive direct measurements of airway epithelial integrity via bronchoscopic biopsies. However, a promising method gaining attention is 'in-vivo cryotechnique' – a valuable novel tool that can be utilized to explore the bronchi in airway disease (i.e., obtain biopsies to examine inflammatory cytokines and epithelial integrity) (78). Moreover, further exploration is warranted to understand how neural adaptations to exercise influence bronchial tone and EIB, and the correlation with sport-specific characteristics. In addition, future studies concerning EIBwa are required to evaluate the therapeutic effects of anticholinergic medication (i.e., determine the relationship between parasympathetic activity and severity of AHR) as well as developing valid methods of assessment to quantify bronchial parasympathetic activity. Finally, whilst non-invasive markers of airway inflammation from induced sputum (e.g., neutrophil count, histamine, eicosanoids, and DAMPs) offer insight into the inflammatory and cellular dynamics associated with EIB, it is important that future studies adopt a consistent approach to sampling, analysis and interpretation.

5. Summary

EIB is a prevalent condition among athletes and individuals with pre-existing asthma, each exhibiting distinct features and mechanisms. The primary acute stimulus provoking EIB is related to the high ventilatory demand associated with intense exercise. In people with EIBa, exercise triggers bronchoconstriction through type 2 inflammatory mediators due to pre-existing underlying AHR and inflammation. In athletes, intense prolonged exercise can cause airway injury, leading to the release of DAMPs that activate an inflammatory response causing bronchoconstriction. Other mechanisms in athletes include autonomic nerve involvement and post-exercise hyperemia. EIB biomarkers have an established role in both clinical assessment and management and offer insight concerning underpinning mechanisms associated with the development and progression of airway pathophysiology. Further high-quality research in this setting remains a priority to achieve the ultimate goal of developing personalized / phenotype-specific treatments for individuals with EIB.

Disclosure statement

The authors declare that they have no conflicts of interest to disclose.

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