

An Update on Exercise-Induced Bronchoconstriction With and Without Asthma

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Exercise-induced bronchoconstriction (EIB) is defined as transient, reversible bronchoconstriction that develops after strenuous exercise. It is a heterogeneous syndrome made up of a spectrum of phenotypes ranging from the asymptomatic military recruit whose condition is detected by diagnostic exercise challenge to the athlete with known asthma to the elite athlete for whom EIB represents an overuse or injury syndrome. If exercise is the only identified trigger for bronchoconstriction, it is called EIB. However, when it is associated with known asthma, then it is defined as EIB with asthma. This review discusses the pathogenesis, presentation, diagnosis, and management of EIB and EIB with asthma.

Introduction

Exercise-induced bronchoconstriction (EIB) is a transient, reversible bronchoconstriction that develops after strenuous exercise. The term *exercise-induced asthma* is no longer used, as exercise does not induce asthma but triggers bronchoconstriction; thus, the more correct term is *EIB with asthma*, which presents with cough, wheezing, chest tightness, pain, and/or shortness of breath. It may be present with posttrace cough in the elite athlete or with nonspecific symptoms of locker room cough, inability to keep up with peers, stomachache, or sore throat in younger athletes or children [1•,2–6]. It is associated with at least 5 to 10 minutes of continuous, usually dehydrating strenuous exercise such as running or cycling more commonly than it is with swimming. EIB with asthma is often the first sign of asthma in up to 90% of patients with that disease and is commonly the

last to resolve with an asthma exacerbation [1•,2–6]. Although recent studies and meta-analyses did not note the impact of swimming up to 20 h/wk, it has been noted to impact elite athletes, who improve when the swimming regimen is discontinued [2–4]. EIB with asthma is a cardinal feature of asthma that usually leads to a timely diagnosis [5]. However, it is commonly under- and over-diagnosed, as the signs and symptoms are nonspecific, and objective pulmonary function testing is necessary to document EIB with asthma [1•,2,5]. As such, EIB with asthma is a reflection of asthma control. Although a history of cough, wheezing, and chest symptoms following vigorous exercise correlates best with EIB with asthma, shortness of breath alone is rarely diagnostic of asthma. Isolated dyspnea indicates that a differential diagnosis that usually includes conditioning but also more rarely cardiopulmonary abnormalities (eg, pulmonary edema and hyperventilation) and upper airway conditions (eg, vocal cord dysfunction) must be considered [1•,2,5]. Athletes often mistake EIB for a lack of conditioning [5]. *Dangerous exercise*, a term coined by Cooper et al. [7], may lead to activation of neutrophils and inflammation (as in the overuse syndrome), circulation of immune cells from the spleen to the gut (as in exercise- and food-dependent anaphylaxis), or even worsening of infection or asthma [7,8]. Denial is common, and under- and overdiagnosis result [1•,2,5]. Rarely, exercise may be accompanied by anaphylaxis, sometimes in conjunction with food (particularly wheat products) and related to acceleration of the gliadin pathway in the gut [9].

However, EIB with asthma must be considered in any athlete—competitive or noncompetitive, recreational or elite—with symptoms of asthma with strenuous exercise. Screening for EIB with asthma is problematic given the need for a standardized and reproducible test for diagnosis that is universally accepted [10,11••].

Diagnosis relies on standardized and reproducible objective challenges, usually with exercise such as a treadmill, cycle, or less reliable but more familiar free running or sports challenge in the field. Direct pharmacologic challenges using a single mediator such as methacholine or histamine are less reliable. Indirect challenges relying on hyperosmolar agents, such as exercise, or investigative

surrogate agents, such as mannitol, hypertonic saline, or eucapnic hyperventilation, are more specific and sensitive because they elicit a broader range of mediators, similar to exercise. However, only exercise challenge of the indirect methods is generally used in clinical practice; the guidelines of the American Thoracic Society and European Respiratory Society are available [1••,11••].

Individuals with EIB with asthma and EIB alone should adhere to a continued healthy lifestyle with modification of exercise regimen only in the most competitive or elite athletes who exercise more than 20 h/wk [4,12]. This review discusses the most contemporary issues related to pathogenesis, diagnosis, and therapy for EIB and asthma.

Epidemiology of EIB and EIB With Asthma

The prevalence of EIB with asthma is determined by the definition; population studied (whether atopic, athletic, or unselected); pulmonary function criteria; exercise load, intensity, and duration; and the environment, with 20% incidence with 10% decline in pulmonary function test, 11% incidence with 12.5% decline, and 9% incidence when using a 15% decline [13,14]. In the general population, the cumulative prevalence is 7% to 20% [15,16•], 13% in middle school and high school athletes [17], and 12% to 23% in high school football players [18]. In a recent meta-analysis, there was a four- to sixfold increase in runners and cyclists compared with swimmers [2]. Although asthma is more commonly diagnosed in elite swimmers than in other competitive athletes, there is no clear causal relationship with swimming, as the studies are cross-sectional and asthma is not more common among noncompetitive or competitive adolescent swimmers. Also, individuals with asthma may choose swimming as a less asthmogenic sport because of their disease [2]. However, 70% to 90% of asthma patients are considered to have EIB, as are about 40% of those with allergic rhinitis [1••]. An estimated 11% of Olympians in 1984 had EIB, 61% of whom won medals [19]. Similar success was noted in the Olympics up through 2008, indicating that EIB with asthma does not impair an active, healthy lifestyle [1••,19].

Pathogenesis: EIB/EIB With Asthma

EIB in individuals with asthma is proposed to be an exaggerated response to airway dehydration in the presence of inflammatory cells and their mediators [20••]. The thermal theory (Table 1) proposed that vasoconstriction of bronchial vasculature in response to airway cooling led to airway narrowing secondary to reactive hyperemia associated with vascular leakage and edema of the airway [20••,21]. Cold air enhances the dry air in the decline in airway function or narrowing reflected in decline in forced expiratory volume in 1 second (FEV₁) [20••,21]. Cold air increases the area that is dehydrated and hyperosmotic, thus enhancing the primary effect of dry air in creating a hyperosmolar environment. There is recruitment of small

Table 1. Evidence of inflammation in exercise-induced bronchoconstriction

Cellular: eosinophils, neutrophils, macrophages, lymphocytes, columnar epithelial cells
Phospholipase
Vascular endothelial growth factor
Angiopoietin-1 and angiopoietin-2
Lipoxin
CD40
RANTES (regulation on activation, normal T-cell expressed and secreted)
Endothelin-1
Mast cell mediators: tryptase, histamine, prostaglandins, leukotrienes

airways (< 1 mm) to condition large volumes of cold, dry air in elite winter athletes such as hockey players or cross-country skiers with repetitive injury to the epithelium and microvascular injury and permeability with leakage of plasma protein. The leakage of plasma protein allows for sensitization of bronchial smooth muscle by plasma protein, leading to airway reactivity to pharmacologic mast cell mediators such as histamine and methacholine. Mast cells surrounding smooth muscles are more enriched in the small airways, leading to a condition called *mast cell myositis*. There is evidence of inflammation with neutrophils in winter athletes, in contrast to the predominance of eosinophils in atopic summer athletes [20••]. The inflammation characteristic of EIB alone in elite athletes is not responsive to inhaled steroids, which suggests overuse injury rather than typical asthma [1••,16•,20••,21–23]. Consistent with this hypothesis, the discontinuation of training results in resolution of EIB alone in elite athletes [4].

The evidence for EIB as an inflammatory process with epithelial injury is reflected by columnar epithelial cells in the airway and diminished prostaglandin (PG)E₂. There is endothelial involvement with the hyperosmolar environment, signaling release of nitric oxide with demonstrable increased vascular permeability, loss of plasma protein, and airway edema that results in airway narrowing. The vascular component is reflected in vascular endothelial growth factor and receptor and angiopoietin-2 factor activity. There is increased activity of *MUC5* as well as lipoxygenase polymorphisms and inflammatory cell infiltrate, including neutrophils, eosinophils, mast cells, columnar epithelial and endothelial cells, and endothelin-1 [20••,21–26]. There is a higher concentration of eosinophils in the sputum of asthma patients with EIB compared with those without EIB. Further evidence of this inflammatory pathogenesis is illustrated by increased expression of CD40 ligand soluble P selectin, RANTES (regulation on activation, normal T-cell expressed and secreted), β -thromboglobulin, serum eosinophil cationic protein, and fractional exhaled nitric oxide (possibly regulated by heat shock protein) [20••,21–26]. Sensitive

assays of induced sputum and urine indicate increased activation of cysteinyl leukotrienes, secreted phospholipase A2 group overexpression, and PG pathway with increased urinary excretion of leukotriene E_4 and the metabolite of PGD_2 [22,24]. Increased sputum histamine, tryptase, and cysteinyl leukotrienes are noted without downregulation of PGE signaling epithelial injury [22]. A relative excess of leukotrienes compared with PGs results in profound bronchoconstriction and airway reactivity to cold, allergens, pollutants, and viral infection [20••,21,22]. The enhanced expression of the mediators, including histamine, which contributes to the early decrease in FEV_1 , and PGs and leukotrienes, which contribute to the prolongation of the decline in FEV_1 in conjunction with airway inflammatory cells, is evidence of the inflammatory process of EIB. However, this inflammatory process alone in elite athletes also does not respond to montelukast [20••,22–26]. Korean studies confirm that polymorphisms affect cytokines (interleukin-13), which support the role of genetics [25]. EIB is refractory to repeated exercise, presumably because of an imbalance in the prostaglandin PGE_2 , a smooth muscle relaxant [20••,27,28]. The refractory period is postulated to be secondary to PG triggered by cysteinyl leukotriene, with cyclic adenosine monophosphate inhibiting mediator release. A refractory period is noted in 50% of asthma patients with EIB. Evidence of mast cell involvement and causality is found with PGD_2 in the urine and mediators in sputum. The mediators in the urine and sputum are induced by hyperosmolar stimuli that simulate exercise. These mediators are inhibited by prophylactic mast cell blockade by cromolyn and formoterol, suggesting mast cell involvement [20••,27,28,29•].

Overuse injury may account for the continuum of EIB/EIB with asthma with more intense, heavier workload of greater than 20 h/wk, which leads to more ongoing lung injury with tenascin [20••,23]. Acute treatment with a β -agonist may be helpful, as it stabilizes the mast cell [27]. However, chronic treatment with a β -agonist results in downregulation and destabilization of the mast cell and in smooth muscle conversion by guanosine triphosphate cross-talk from smooth muscle relaxation to constriction [20••]. Elite athletes exercising strenuously may be immune suppressed (open window theory) for a transient period after exercise. Therefore, they may be more vulnerable to upper respiratory illness, which may enhance airway hyperreactivity [7]. The refractory period, which is secondary to PGE_2 and blocked by indomethacin, and the late phase, which is less predictable or controversial, differentiate the pathogenesis and management of EIB from those of chronic asthma [20••,21,27,28,29•].

The effect of the environment on EIB is demonstrated by studies indicating that ozone may impact asthma in athletic children [30–32]. Varsity college athletes may have similar outcomes with high levels of ventilation [33]. Particulate matter has been noted to impact EIB in ice rinks with Zambonis and in athletes who exercise near

heavy traffic with cars and trucks, with isoprostane noted in exhaled breath condensate [30–32,34]. Reactive oxygen species generated by fossil fuel combustion and emission lead to oxidant consumption and stress with glutathione S-transferase, the antioxidant defense found in high concentration in the lung [32]. A *GSTP1* polymorphism may be associated with new onset of asthma and EIB in children who play team sports. Reduced glutathione may be associated with oxidant stress in chronic obstructive pulmonary disease and enhancement of leukotriene synthesis. Oxidant stress in EIB and chronic obstructive pulmonary disease may improve with provision of a precursor, *N*-acetylcysteine, which blocks nuclear factor- κ B and interleukin-8 [32].

Diagnosis

As noted, EIB is one of the first signs of asthma in children and one of the last to improve with inhaled corticosteroid use [29•]. The prevalence varies with the intensity and duration of the exercise stimulus as well as the population surveyed (recreational, competitive, or elite athlete). This prevalence is also affected by the sex of the population, rural or urban setting, the presence of atopy and asthma, the treatment, and the criteria used for diagnosis (ie, decline in $FEV_1 \geq 10\%$). The prevalence varies from 19% in schoolchildren to 50% in elite cross-country skiers [21,29•].

The diagnosis of EIB with asthma requires objective pulmonary function testing, preferably using exercise challenge or a hyperosmolar surrogate. Several studies demonstrated that symptoms or history alone lack sensitivity and specificity [33,35–38]. Up to 50% of athletes may have a positive history and negative exercise challenge, and a similar percentage may have positive exercise challenge in the absence of symptoms, indicating a problem with perception of bronchospasm [33,35]. Studies in large populations of children have long demonstrated the validity of free running challenge, even if symptoms are not reliable in the diagnosis or prediction of EIB/EIB with asthma, and even in children 3 to 7 years of age and in rural and urban settings [38–41]. However, screening is not possible because of lack of consensus on the appropriate challenge model, pulmonary function cutoff, definition of EIB/EIB with asthma, and utility for management [10].

Two types of challenge exist: 1) the direct pharmacologic challenge characterized by methacholine or histamine and 2) indirect challenge using exercise or a surrogate measure such as mannitol, hypertonic saline, or hyperventilation. The direct challenge is less sensitive and specific because it uses only a single mediator, such as histamine. The indirect challenge is more sensitive and specific, as it releases the entire repertoire of mediators, including PGs and leukotrienes, and is reflective of the pathophysiology of EIB with asthma. Exercise challenges such as bicycle and treadmill are easily monitored, whereas free running and sports challenge are difficult to monitor but more asthmogenic, inexpensive, familiar,

and sensitive [11••,16•,17,21,29•]. The use of cycling is preferred in the laboratory, as it is safe, and evaluation of ventilation and heart rate is more reproducible than in situations in which a patient is running on a treadmill or free running [11••,16•,17,21,29•]. The duration of exercise is recommended to be at least 6 minutes in children and preferably 8 minutes in adults with intensity of at least 80% maximum heart rate or more than 21 times the FEV₁ that represents 50% to 60% of predicted maximum with 50% relative humidity at 20°C [29•]. The intensity for elite athletes is at least 90% to 95% maximum heart rate [29•]. For children, 90% maximum heart rate is more sensitive [11••,29•]. A reproducible decline in FEV₁ by at least 10% after challenge with monitoring for at least 30 minutes after exercise is considered diagnostic by the American Thoracic Society. However, no absolute consensus exists, as this is based on statistical probability and standard deviation, as the decline in FEV₁ has a normal distribution in a large population [16•,20••,21].

Because the exercise challenge is difficult to reproduce, particularly with athletes, the surrogates to exercise are used. These include hyperosmolar agents, particularly mannitol, or dry air and eucapnic hyperventilation, the official Olympic screening method. Mannitol is efficient, reproducible, less expensive, and more sensitive and specific for monitoring the severity of EIB and the success of therapy [11••,29•]. These hyperosmolar challenges are still investigational in the United States, but US Food and Drug Administration approval for mannitol is pending [11••,29•]. There is no consensus gold standard; the combination of the challenge and monitoring of biomarkers such as nitric oxide and exhaled breath condensate may be the most reliable indices [1••]. The utility of a combination of fractional exhaled nitric oxide and pulmonary function testing in evaluating children for EIB has been demonstrated. Negative fractional exhaled nitric oxide effectively ruled out EIB [1••]. These diagnostic methods in conjunction with pulmonary function testing discriminate EIB from differential diagnoses, which include airway abnormalities such as vocal cord dysfunction; lack of physical conditioning; or other cardiopulmonary conditions, such as exercise hyperventilation or pulmonary edema, rhythm disturbance, or gastroesophageal reflux, which occur during exercise [10,21,29•]. This is in contrast to EIB, which occurs after exercise.

Therapy

Preventive treatment with short-acting β -agonists prior to exercise is the first line of therapy for EIB with asthma (Table 2) [1••,16•,21,29•,42–44]. Trials of montelukast have provided variable results [45–48]. In one trial, montelukast provided measurable protection against EIB in asthma patients 15 to 44 years of age, with onset of action within 2 hours [46].

Table 2. Anti-inflammatory treatment of exercise-induced bronchoconstriction per NHLBI guidelines for asthma

SABA/LABA as needed only, up to 4 times/wk

Nonsteroidal treatment

Inhaled steroids

Combination treatment

Leukotriene modifiers

LABA—long-acting β -agonist; NHLBI—National Heart, Lung, and Blood Institute; SABA—short-acting β -agonist.

Comparing albuterol with montelukast in 11 children with asthma, Raissy et al. [44] documented that both were more effective than placebo. Albuterol was significantly more effective than montelukast. Stelmach et al. [45] demonstrated in a placebo-controlled study in children that combinations including inhaled steroids and long-acting β -agonists (LABAs) with montelukast were more effective than those without it. Repeated combination (inhaled steroid and LABA) therapy over 4 weeks in children and adults led to a decline in response to albuterol for rescue, even with inhaled steroids [1••,13,21,45–50]. This tachyphylaxis does not occur with leukotriene modifiers such as montelukast [1••,16•,21,29•,45–47]. Although montelukast is apparently effective in a subset of patients with EIB with asthma, no predictive indices exist, and it is most effective in individuals not controlled with as-needed short-acting β -agonists. These agents diminish the severity of EIB and increase the recovery from persistent EIB, with restoration of lung function within 10 minutes [29•,45–47]. Pharmacogenetics may play a role in the variability of response to montelukast, as indicated in Korean children [48]. Daily therapy with β -agonists should be avoided if possible to avoid tachyphylaxis.

Per National Heart, Lung, and Blood Institute guidelines, inhaled steroids and a combination of LABAs and inhaled steroids are indicated for moderate to severe asthma, as EIB is an indicator of underlying asthma [42]. Inhaled steroids have been effective as monotherapy in asthmatic children with good pulmonary function and in adults, as they decrease the decline in FEV₁ with exercise [29•]. In individuals who do not have normal lung function with moderate to persistent asthma, combination therapy is very effective in the prophylaxis of EIB [16•]. LABAs are also effective on an as-needed basis, and there is little difference between salmeterol and formoterol in onset of protective outcome [50].

Tolerance occurs to the duration of protection from EIB and was not prevented through use of inhaled corticosteroids [45–47]. LABAs are thus recommended only as needed, preferably three or four times per week [29•].

Sodium cromoglycate (2, 10, or 20 mg) and nedocromil sodium (usually 4 or 8 mg) provide 50% to 80% protection from EIB and enhance recovery. They are effective immediately before exercise [1••,16•,29•,42].

Evaluation by appropriate skin test or specific in vitro IgE and treatment of atopy with nasal steroid, avoidance of allergens, and immunotherapy are also recommended, as 40% to 50% of allergic rhinitis patients have asthma related to exercise [16•].

Nonpharmacologic therapy, including warm-up and warm-down to encourage a refractory period, may be helpful. In one study, strenuous warm-up in conjunction with bronchodilator use was more effective than either intervention alone [29•]. The use of masks and mouthpieces that trap expired water and allow rebreathing has been successful [29•].

Exercise within the hour of previous exercise allows the individual to become refractory. About 50% of individuals will have less than half the severity of response when the exercise is repeated within the hour [29•]. Physical training is also encouraged and is associated with increasing cardiovascular fitness with increased oxygen consumption, decline in heart rate, and ventilation. The increase in fitness therefore will increase the threshold for EIB, impacting on the ventilatory rate, a primary determinant of EIB severity. Warm-ups and sprints increase the rate of delivery of water to the airway mucosa by enhancing bronchial vascular flow. This allows the airways to better adapt to the dehydrating impact of hyperpnea [1•,16•,20•,21–23,29•].

Investigational therapy with fish oil, low-sodium diet, and increased vitamin C intake has been demonstrated to decrease EIB and urinary inflammatory markers in small trials [1•]. Environmental factors inclusive of diet and avoidance of inhalant allergens in the atopic individual with EIB should be considered in the treatment plan [1•].

Conclusions

Proper diagnosis and management of EIB with asthma and EIB alone can minimize or eliminate impairment and thus permit a normal, healthy lifestyle. EIB with asthma can be readily treated with pharmacotherapy for asthma as well as appropriate warm-up and warm-down, breathing through the nose, and therapy for inhalant allergy [1•,16•,29•]. These measures will allow and encourage asthmatic individuals to exercise as part of a healthy lifestyle. EIB has been over- and underdiagnosed, but use of objective testing with pulmonary function and exercise challenge whenever possible per International Olympic Committee Medical Commission guidelines should alleviate these problems [11•,16•,29•]. EIB alone in the elite athlete should be managed with appropriate limitation of training and exercise prescription with cross-training if necessary [4,12,20•,21].

Disclosure

No potential conflict of interest relevant to this article was reported.

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