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Review Article

Mechanisms of disease for the clinician: exercise-induced bronchoconstriction

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ABSTRACT

Objective: To review the literature regarding the pathophysiology of exercise-induced bronchoconstriction (EIB).**Data Sources:** The databases of PubMed, Ovid MEDLINE, and Scopus were searched for articles using the subject headings and/or keywords *asthma*, *exercise-induced/etiology*, *exercise*, *mechanism*, *pathogenesis*, and *bronchoconstriction*.**Study Selection:** Articles were selected based on their relevance to the focus of this review, with emphasis on the specific pathophysiologic mechanisms of EIB.**Results:** EIB occurs in response to the loss of water from the lower airways that results from heating and humidifying large volumes of air in a short period. The resulting hyperosmolar environment activates various cellular mechanisms to release mediators from mast cells, eosinophils, epithelial cells, and sensory nerves. These mediators, in turn, lead to airway smooth muscle contraction and bronchoconstriction. Airway hyperresponsiveness in elite athletes may develop from a process of airway injury and changes in the contractile properties of airway smooth muscle.**Conclusion:** EIB commonly affects individuals with and without clinically recognized asthma, especially those who participate in competitive athletics. Through years of research, the pathophysiology of EIB is now better understood and involves a complex interaction between several different cell types and mediators. Continued research to improve the knowledge regarding the mechanisms of EIB should aid the identification, diagnosis, and treatment of this common condition.

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Introduction

Exercise-induced bronchoconstriction (EIB) is defined as the transient, reversible narrowing of the lower airways that follows vigorous exercise in the presence or absence of clinically recognized asthma. The term *exercise-induced asthma* is no longer used because exercise does not cause asthma but rather is a trigger of bronchoconstriction.¹ This article reviews the literature regarding the pathophysiology of EIB. The databases of PubMed, Ovid MEDLINE, and Scopus were searched for articles using the subject headings and/or keywords *asthma*, *exercise-induced/etiology*, *exercise*, *mechanism*, *pathogenesis*, and *bronchoconstriction*. Articles were selected based on their relevance to the focus of this review, with emphasis on the specific pathophysiologic mechanisms of EIB.

The diagnosis of EIB typically requires a decrease in forced expiratory volume in 1 second (FEV₁) at any 2 consecutive time points within 30 minutes after exercise of 10% to 15% of the pre-exercise FEV₁ value.^{1–3} EIB is a manifestation of airway hyperresponsiveness and is often the first sign of asthma to appear and the last to resolve with an asthma exacerbation.^{1,4} EIB is reported to

occur in up to 90% of individuals with asthma and in 40% of those with allergic rhinitis.⁴ Individuals with more severe or poorly controlled asthma are more likely to exhibit EIB than those with less severe or well-controlled disease.¹ In the general population, the cumulative prevalence of EIB ranges from 7% to 20%.⁴ The prevalence of EIB in competitive athletes appears to be higher than in the general population, with ranges up to 50%, depending on the type of sport, environmental conditions in which the exercise is performed, and the maximum exercise level.¹

Stimulus for EIB

EIB occurs in response to the loss of water from the airways that results from heating and humidifying large volumes of air in a short period. The major determinants for the severity of the airway response include the water content of the inspired air and the level of ventilation achieved and sustained during exercise.^{1,5}

Under most environmental conditions, inspired air needs to be conditioned, that is, heated and humidified to physiologic conditions (ie, 37°C with 44 mg H₂O/L), before entering the lower airways. The amount of conditioning required depends on the water content as determined by the temperature and humidity of the inspired air and by the amount of ventilation. Heat and water move from the mucosa to the inspired air directly due to local

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temperature and vapor-pressure gradients and inversely with the linear velocity of the airflow. During this process, cooling of the airways occurs.⁶ At resting ventilation, air is typically fully conditioned in the upper airway as it passes over the nasal mucosa. With vigorous exercise, ventilation increases above 30 L/min, and a switch from nasal to mouth breathing occurs.^{1,5,7} Thus, with increased ventilation, more unconditioned air reaches the lower airways, which are then required to complete the conditioning process.⁵

In the lower airways, the immediate source of water to humidify the air is the airway surface liquid lining the epithelium, also known as the periciliary fluid layer. The epithelium is an absorptive surface during resting conditions but must become a secretory surface during exercise to replenish the airway surface liquid.⁸ The airway surface liquid has an osmolarity of 290 to 320 mOsm and contains sodium, chloride, potassium, and calcium ions. During exercise, when ventilation exceeds 40 L/min, water must be rapidly replaced on the airway epithelium to prevent dehydration and an increase in osmolarity. Rapid water replacement occurs by condensation of water from exhaled air, containing gas from the alveoli, which is now warmer than the mucosa, on to the cooled airway surface. Additional water replacement occurs through an osmotic gradient from the bronchial circulation to the airway epithelial surface to restore normal osmolarity.⁵ However, even with these homeostatic mechanisms, mathematical models estimate that approximately 40% of the total water loss per minute comes from the lower airways, at conditions of 22°C to 26°C, 40% humidity, and ventilation at 60 L/min.^{5,9,10} This evaporative water loss that occurs in response to high ventilation during exercise is the key initiating stimulus for EIB.

Pathophysiologic Mechanisms for EIB

Two main theories have been used to explain the mechanism of EIB: the thermal theory and the osmotic theory (Fig 1). These 2 theories differ in the relative importance placed on the consequences of airway water loss. The thermal theory proposes that airway cooling from evaporative water loss causes a vasoconstriction of bronchial vasculature. On rewarming, airway narrowing will occur due to the mechanical effects of vascular engorgement, vascular leakage, and edema of the airway wall.^{4,5,11,12} Thus, in this scenario, airway narrowing would occur as a direct consequence of

vascular events and would be unrelated to mediator release or airway smooth muscle contraction. In contrast, the osmotic theory proposes that the primary effect of airway water loss is increased osmolarity of the airway surface liquid, which extends to include the airway epithelial cells and submucosa. This hyperosmolar environment activates cellular mechanisms to release various mediators. These mediators, in turn, cause airway smooth muscle contraction and subsequent airway narrowing.¹³

The thermal theory does not account for many observations of EIB. Findings demonstrate that airway cooling and rewarming are not essential events for EIB to occur because inspiring hot, dry air (>37°C) can cause severe EIB in individuals with asthma.^{5,14–16} In addition, EIB can be markedly inhibited or completely prevented when inspired air is at body temperature and fully saturated with water during exercise.^{5,8,17,18} Additional studies using gases of different heat capacities confirmed that water loss is more important than heat loss for EIB to occur.¹⁹ Exercise in warm, dry conditions has been found to cause a reduction in humidity of expired air, which is consistent with an increase in osmolarity of the airway surface liquid,²⁰ and dehydration can result in an increase in ion concentration and osmolarity in the upper airways.²¹ Finally, numerous studies have demonstrated the association of several mediators with EIB. With all this accumulated evidence, the hyperosmolar explanation for the pathogenesis of EIB is now considered the leading theory for EIB.¹

Mediators of EIB

Several mediators are involved in the pathogenesis of EIB, resulting in airway inflammation and epithelial injury (Fig 2). Eicosanoids appear to play a significant role in the inflammatory process.²² Eicosanoids are lipid mediators formed from the phospholipid membrane component of arachidonic acid (AA) and include leukotrienes (LTs), hydroxyeicosatetraenoic acids, and prostaglandins.²³ Individuals with asthma have increased levels of LTs, such as cysteinyl leukotrienes (cysLTs), in the airways, and inhalation of cysLTs reproduces several features of asthma.^{23–25} Members of the PG family include prostaglandin D₂ (PGD₂), which has bronchoconstrictive properties,²⁶ and prostaglandin E₂ (PGE₂), which has a bronchodilating and bronchoprotective role.²⁷

Higher levels of cysLTs and PGD₂ have been demonstrated in induced sputum after exercise challenge in asthmatic patients with EIB compared with those without EIB.²⁸ These increased levels of cysLTs and PGD₂ in the airways are sustained after exercise and occur with a concurrent decrease in the level of PGE₂.^{28,29} At baseline in individuals with EIB, the level of PGE₂ relative to the amount of cysLTs is reduced when compared with those without EIB.³⁰ The ratio of cysLTs to PGE₂ increases significantly from pre-exercise to postexercise challenge, a situation favoring bronchoconstriction after exercise challenge.²⁸ An increase in urinary excretion of 9 α ,11 β -PGF₂, a metabolite of PGD₂, occurs after exercise and can also be found in sputum after exercise.^{5,31,32} The change in levels of 9 α ,11 β -PGF₂ from baseline is significantly associated with the percentage decrease in FEV₁.³¹

Eicosanoid biosynthesis is regulated by phospholipase A₂ (PLA₂), which hydrolyzes membrane phospholipids and releases unesterified AA, the precursor to the eicosanoids.³³ Cytosolic PLA₂ α (cPLA₂ α) is necessary for eicosanoid formation. A group of secreted PLA₂ enzymes (sPLA₂s), in the presence of cPLA₂ α , has been found to augment AA production over cPLA₂ α alone and may preferentially direct the eicosanoid synthetic pathway toward LT production. Specifically, sPLA₂ groups X (sPLA₂-X) and XIIa predominate at the level of gene expression and are primarily found in columnar epithelial cells and bronchial macrophages. In particular, sPLA₂-X is the most potent of the sPLA₂s at releasing AA. Increases in sPLA₂-X protein can be found in induced sputum supernatant and in

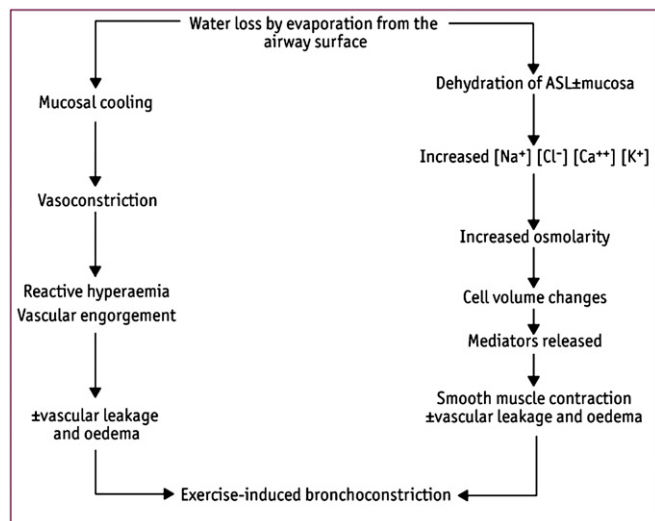


Figure 1. Exercise-induced bronchoconstriction pathophysiologic theories: thermal (left) and osmotic (right). ASL indicates airway surface liquid. Reprinted with permission from Anderson and Kippelen.⁵

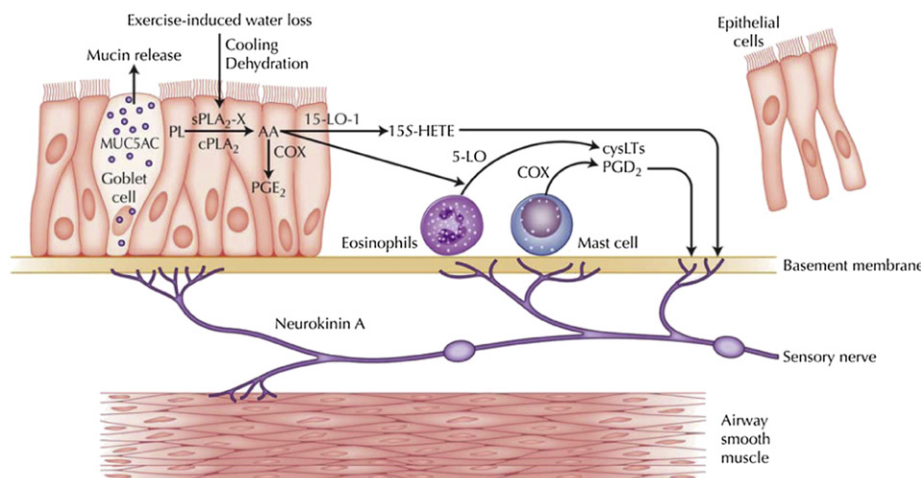


Figure 2. Disease model of exercise-induced bronchoconstriction (EIB) pathogenesis. Asthmatics with EIB have increased concentrations of shed epithelial cells, cysteinyl leukotrienes (cysLTs), and cystT/prostaglandin E_2 (PGE_2) ratio in induced sputum. Exercise challenge initiates the production of cysLT, PGE_2 , and 15S-hydroxyeicosatetraenoic acid (15S-HETE) and a reduction in PGE_2 . An increase in secreted phospholipase A_2 group X (sPLA $_2$ -X) may increase the release of arachidonic acid (AA) by the epithelium or by adjacent inflammatory cells. Contraction of the airway smooth muscle and mucin release occurs in part through retrograde axonal transmission in sensory nerves that release neurokinin A. 15-LO-1 indicates 15-lipoxygenase-1; 5-LO, 5-lipoxygenase; COX, cyclo-oxygenase; cPLA $_2$, cytosolic PLA $_2$; MUC5AC, mucin 5AC; and PL, phospholipids. Reprinted from Hallstrand and Henderson with permission of Springer Science and Business Media.²²

epithelial cells after exercise challenge, thus providing an explanation for the high levels of cysLTs and other eicosanoids in EIB.^{22,33}

Mast cells and eosinophils are key sources of cysLTs and other eicosanoids in EIB. The amount of eosinophilia in induced sputum has been correlated with the degree of EIB severity.³⁴ Eosinophilic cationic protein (ECP) is released from eosinophils into the airways after exercise challenge, and ECP concentrations vary with EIB severity under different conditions.²⁹ Levels of histamine and tryptase are also elevated after exercise challenge,^{22,28} and mast cell genes have been found to be overly expressed in asthmatic patients with EIB compared with those without EIB.³⁵ Antihistamines reduce the amount of histamine released after exercise challenge, and histamine appears to be responsible for bronchoconstriction soon after challenge, whereas cysLTs are responsible for sustained bronchoconstriction.^{22,36} Pharmacologic inhibition of the cysLT $_1$ receptor along with antihistamine reduces the severity of decrease in FEV $_1$ and reduces the release of inflammatory mediators into the airways.^{22,28} This reduction in EIB severity by cysLT $_1$ inhibition alone is incomplete, thereby suggesting that other bronchoconstrictive mediators are involved and/or a reduction in bronchoprotective mediators occurs.^{22,37}

In addition to mast cells and eosinophils, the epithelium may also be involved in the generation and regulation of mediators involved in EIB. Adenosine resulting from adenosine triphosphate in the epithelium has been measured in exhaled breath condensate after exercise, and measured adenosine levels correlate with EIB severity.^{38,39} Adenosine and adenosine triphosphate are key regulators of the depth of the airway surface fluid layer and via A_{2b} receptors act on mast cells to release mediators.^{5,40} The epithelium also expresses 15-lipoxygenase-1, which synthesizes the bronchoconstrictive mediator 15S-hydroxyeicosatetraenoic acid. Exercise challenge has been found to increase the level of 15S-hydroxyeicosatetraenoic acid in the airways of asthmatic patients with EIB.²³ The epithelium is also a major source of PGE_2 , which has been found to be bronchoprotective and can inhibit EIB when administered by inhalation. Thus, through close contact interactions with inflammatory cells, the epithelium may regulate the balance between the release of bronchoconstricting eicosanoids and mechanisms, which reduce the synthesis of PGE_2 .^{22,28}

Additional mediators that may contribute to bronchoconstriction in EIB are released from sensory airway nerves. These sensory nerves are activated by eicosanoids, such as cysLTs, in the

airway. Activated sensory nerves release neurokinins, which lead to bronchoconstriction and mucous release.²² Mucin 5AC (MUC5AC) is the predominant gel-forming mucin of goblet cells. The gene expression and level of MUC5AC in the airways increases after exercise challenge and is associated with EIB severity. Associations between levels of MUC5AC and cysLTs and between levels of cysLTs and neurokinin A have been demonstrated in the airways post-exercise challenge, which indicates that MUC5AC release may occur by a mechanism of cysLT activation of sensory airway nerves.⁴¹

EIB and Airway Injury in the Elite Athlete

Airway injury represents another mechanism that may play an important role in the development of EIB and airway hyperresponsiveness in elite athletes (Fig 3). During intense physical activity conducted over prolonged amounts of time, the smaller lower airways are increasingly recruited for conditioning large volumes of air. This process is repetitive because of the nature of elite athletic training; therefore, there is increased risk of dehydration injury to the airway epithelium.¹³ Epithelial repair of this airway injury involves microvascular leak and plasma exudation.⁴² Epithelial injury results in a reduced capacity to move water to the airway to respond to a hyperosmolar stimulus.⁴³ With repeated injury, a larger airway surface area will need to be recruited in the conditioning process, thereby causing continued progression of the airway injury. Airway hyperresponsiveness in elite athletes may develop as the contractile properties of airway smooth muscle change and become more sensitive to stimuli due to repeated exposure to plasma-derived products.^{44,45} This type of injury process may explain the high levels of airway hyperresponsiveness to methacholine reported in endurance athletes, especially those who perform in cold climates and those athletes without EIB or symptoms.^{46,47} Supportive evidence for the occurrence of this type of airway injury process includes documentation of normal airway responsiveness when out of season⁴⁸ or after retirement.⁴⁹ Thus, this reversal of airway hyperresponsiveness would suggest that this type of airway injury does not involve airway remodeling and likely does not predict chronic disease.^{44,50}

Application of Pathophysiologic Mechanisms to Diagnose EIB

Diagnosing EIB in the laboratory can be difficult, and the type of protocol used for diagnosis must consider the stimulating and

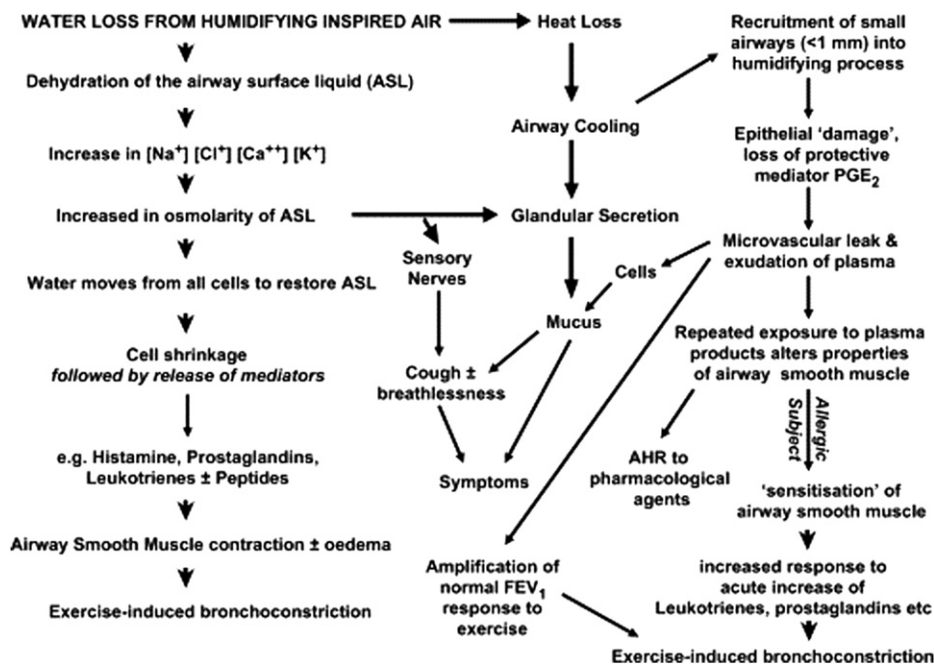


Figure 3. Flow chart describing acute events leading to exercise-induced bronchoconstriction (EIB) in the patients with classic asthma (left) and events leading to development of EIB in the athlete (right). AHR indicates airway hyperresponsiveness; FEV₁, forced expiratory volume in 1 second; and PGE₂, prostaglandin E₂. Reprinted with permission from Anderson and Kippelen.⁴⁴

mechanistic factors for EIB.^{5,45} To elicit dehydration of the airway surface liquid and cause a transient increase in its osmolarity, the rate of water loss must exceed the rate of return in the first 10 generations of airways. In general, the drier the inspired air and the higher the ventilation sustained during exercise, the less likely a false-negative test result will occur.⁵ Exercise at suboptimal intensity or duration or a high water content of inspired air (>10 mg H₂O/L equivalent to 23°C and 50% humidity) can cause false-negative test results.⁴⁵ To provoke EIB, the exercise intensity in the first 2 minutes needs to be sufficient to raise ventilation to at least 17.5 times FEV₁, preferably more than 21 times FEV₁, and the heart rate to greater than 80% of predicted maximum. This exercise intensity must be sustained for 6 minutes in children and 8 minutes in adolescents and adults to optimize the probability of an accurate positive test result. Target ventilation is easier to achieve with running as opposed to cycling.⁵ A source of dry air is required to ensure low water content of the inspired air. The inspired air also may need to be cooled to provoke EIB in some individuals.⁴⁵

As the exercise intensity rapidly increases, ventilation increases as well, and thus in the span of a few minutes, more generations of lower airways are recruited in the conditioning process. Drier inspired air coupled with lower temperatures speeds the recruitment of lower generations of airways to condition the air.⁵ If ventilation increases too slowly, the airways become refractory to EIB-stimulating factors at higher ventilations.⁵¹ It has been demonstrated that a 20-minute warm-up at submaximal intensity or 30-second repeated sprints cause refractoriness to any following vigorous exercise.^{52,53} The precise mechanisms for this refractory period are not fully understood but may be caused by a number of factors, including depletion of mast cell mediator stores, increased circulation of protective prostaglandin, and airway smooth muscle receptor desensitization to mast cell mediators.⁵⁴ Even when the multiple factors affecting an exercise challenge are taken into account, a natural variability in the airway response to exercise is present such that a single negative test result may not be sufficient to exclude a diagnosis of EIB. This variability is particularly evident for individuals with exercise symptoms but without a definite diagnosis of asthma.⁴⁵

To surmount the many technical issues involved with optimizing exercise intensity, surrogates of exercise can be used to identify EIB. Many laboratories now use eucapnic voluntary hyperpnea (EVH) challenge, whereby target ventilation levels up to 30 times FEV₁ can be achieved in the first 30 seconds and easily sustained for 6 to 8 minutes. To maintain eucapnia, a normal carbon dioxide level, the EVH test requires inhaling a dry gas mixture containing 4.9% to 5% carbon dioxide, 21% oxygen, and balanced nitrogen. The high ventilation rate and dry gas mixture result in a low false-negative rate for diagnosing EIB.^{5,45}

Other surrogates of exercise include aerosols of hyperosmolar agents, such as 4.5% saline and mannitol dry powder, which mimic the dehydrating effects of respiratory water loss on the osmolarity of the airway surface liquid.⁵ Mannitol has been demonstrated as a good alternative to EVH for identifying EIB. Mannitol challenge has a number of advantages over exercise or EVH challenges, such as the dose response nature of the test, ease of application, absence of specialized equipment, and general widespread availability.⁵⁵

The diagnostic method used to test for EIB is critical in making a correct diagnosis and thus developing an appropriate treatment strategy. Indirect challenges, such as exercise, EVH, nebulized hypertonic saline, and inhaled mannitol, appear to be more effective in identifying EIB than direct challenges, such as methacholine or histamine. Indirect challenges cause inflammatory cells to release mediators that provoke airway smooth muscle contraction, which thereby reflects the degree of airway inflammation that is present. In contrast, direct challenges act directly with airway smooth muscle receptors to cause bronchoconstriction independent of airway inflammation.³

Conclusion

EIB commonly affects individuals with and without clinically recognized asthma, especially those who participate in competitive athletics. The initial stimulus for EIB stems from airway water loss that occurs when the lower airways must condition large volumes of air in a short period. The resulting hyperosmolar environment

activates various cellular mechanisms to release numerous mediators, which, in turn, lead to airway smooth muscle contraction and bronchoconstriction. Improved knowledge regarding the mechanisms of EIB should aid the identification, diagnosis, and treatment of this common condition.

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