

Where to from Here for Exercise-Induced Bronchoconstriction

The Unanswered Questions

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KEYWORDS

• Injury • Epithelium • Water transport • Mast cells • Sensory nerves • Eicosanoids

KEY POINTS

- Injury of the epithelium is important in the development of exercise-induced bronchoconstriction (EIB).
- Airway injury in elite athletes may relate to the large volumes of air inspired during training.
- Dysregulation of water movement and balance in the airways may contribute to the pathology of EIB.
- Mast cells, eosinophils, and sensory nerve cells are all likely to be involved in EIB.
- Cysteinyl leukotrienes are the major mediators of EIB with prostaglandins (PGs) likely to play a role in attenuating (PGE₂) or enhancing (PGD₂) the response.
- Refractoriness after exercise may relate to desensitization of airway receptors rather than depletion of mediators.
- New and more sensitive technologies for assaying mediators and measuring changes in pulmonary function are becoming available and will improve our understanding of EIB.

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- Mild EIB may represent a different phenotype than more severe EIB and involve different mechanisms.
- EIB in children has faster onset and recovery compared with adults and the mechanism for this may relate to remodeling.

WHAT IS THE ROLE OF INJURY OF THE EPITHELIUM IN EXERCISE-INDUCED BRONCHOCONSTRICTION?

In recent years, a concept has emerged placing an abnormal airway epithelium at the center of asthma development and progression.^{1,2} In asthmatic patients, properties of the epithelial barrier are believed to be impaired as a result of both intrinsic (eg, genetic polymorphisms)³ and environmental factors (such as respiratory viruses, cigarette smoke, pollution, and allergens).^{4–7} Susceptibility of the epithelium to damage by environmental agents followed by incomplete repair is believed to lead to a dysregulated repair process, with secretion of biologically active substances that drive the structural and inflammatory changes characteristic of asthma.⁸ *In vitro* studies have recently confirmed that (1) the bronchial epithelial barrier in asthma is compromised (facilitating penetration of allergens and other noxious airborne particles) and (2) bronchial epithelial cells from asthmatic patients are inherently dysfunctional in their ability to repair wounds.^{9,10} Whether these pathologic changes can be observed specifically in the airways of patients with exercise-induced bronchoconstriction (EIB) is not known; however, the number of ciliated epithelial cells shed into the airway lumen is higher in patients with asthma who have EIB.¹¹

Although 10% of the population have EIB, this percentage is higher in elite athletes, making it one of the most common morbidities in this group.¹² High minute ventilation in conditions with dry air and a high pollen count may be factors that increase the incidence of EIB.^{13–15} There is a connection between the incidence and the number of training years and intensity of the sport¹⁶ suggesting that repetitive injury may play a role. It has been proposed that repetitive epithelial injury and the repair process that follows in elite athletes contributes to the development of EIB, possibly as a result of a change in contractile properties of the bronchial smooth muscle.^{17,18}

Previous investigations *in vivo* based on indirect measures of airway epithelial integrity (ie, the concentration of columnar epithelial cells in induced sputum) suggest that injury to the airway epithelium is a key susceptibility factor for asthma with EIB.¹⁹ Animal-based^{20,21} and human-based studies^{11,22–24} suggest that exercise hyperpnea can lead to a transient loss of the integrity of the airway epithelial barrier. However, confirmation is required on whether the airway epithelium of patients with EIB (with and without asthma) is structurally and functionally abnormal.

Support for a central role of injury of the airway epithelium in EIB is important in that it may prompt a novel therapeutic approach to treatment. Whereas the currently recognized treatments for EIB (eg, inhaled β_2 -agonists and inhaled corticosteroids [ICS]) act mainly downstream from the airway injury (regulating the inflammatory process, mucus secretion, and airway hyperresponsiveness), drugs that help to restore normal epithelial function could potentially prevent the inception of the disease and/or alter its course. New therapeutic agents possibly include drugs such as epidermal and keratinocyte growth factors that enhance the ability of the epithelium to withstand environmental challenge and/or to restore the barrier functions.^{25,26}

IS THE AIRWAY SURFACE FLUID VOLUME DYSREGULATED?

During exercise, strict regulation of the airway surface liquid is required for effective mucociliary transport, and for humidifying the inhaled air to prevent dehydration of the distal airways.²⁷ Mathematical models suggest that, during exercise, the rate of water lost by evaporation can exceed the rate of water return with a net loss of water in some generations of airways.^{28,29} Breathing dry air at high flow decreases mucociliary clearance to a greater degree in asthmatic individuals than in healthy people.²⁷ It is possible that an increase in basement membrane thickness in those with asthma³⁰ may contribute to a slower rate of return of water to the airway surface but this has not been investigated. Treatment with ICS can reverse the changes in thickness³¹ and the same treatment reduces the severity of EIB. Several lines of human-based research suggest that disorders of water transport may be a contributor to EIB. A problem in airway fluid regulation has been proposed to lead to mucus hypersecretion and mucosal edema,³² and in exacerbation of the dehydration stress to the airways during exercise hyperpnoea.^{33,34} It has been proposed that the protective effect of the cromones may play a role in epithelial volume regulation through an action on chloride ion channels.³⁵

Davis and colleagues³⁶ prospectively analyzed the effect of inhaling dry air in a canine model of EIB and found that exposure to dry air leads to an inflammatory response and remodeling in this model. In elite skiers, a similar effect from frequent exposure to dry air occurs and an increase in basement membrane thickness has been reported that is similar to asthmatics.³⁷ Although almost all athletes developed an increase in the thickness of the basement membrane, almost half of the population did not develop EIB or asthmalike symptoms. The reasons why some individuals respond to dry air exposure in such a way that leads to asthma is not fully understood. The early identification of those who will or who will not develop EIB or airway hyper-responsiveness would enable early intervention to prevent further pathologic conditions.

WHAT IS THE ROLE OF AQUAPORINS?

The airway surface liquid volume is regulated by active ion transport and the passive movement of water through membrane water channels called aquaporins (AQPs).³⁸ There are some differences among species regarding these channels, but there is evidence that AQPs 3 and 4 are predominantly located on the basolateral surface of ciliated and basal epithelial cells, respectively, whereas AQP5 may be located on the apical membrane. Dynamic regulation of expression of some of the AQP subtypes (particularly AQP5) may be involved in restoring the airway surface volume in response to changes in osmolarity.³⁹ *In vitro* studies indicate that hypertonic stress induces AQP1 and AQP5 expression,^{39,40} therefore it is possible that a dysregulation of AQP expression contributes to EIB and this needs to be investigated.

DOES THE SWIMMING POOL ENVIRONMENT CONTRIBUTE TO AIRWAY INJURY?

The ambient levels of many byproducts resulting from the use of different disinfectants including ozone, chlorine, and bromine are not always measured in pool environments, despite existing recommendations.⁴¹ Uncertainties still exist on the effect of these byproducts on health, either genotoxic, toxicologic, or carcinogenic, when they are repeatedly inhaled or absorbed at various concentrations. Potential genotoxic effects have recently been suggested after regular exposure to chlorinated swimming pools but further studies should determine the relative risk of such exposures.⁴²

The relationship between trichloramine (NCl_3) concentrations in the swimming pool environment and upper or lower airway injury need to be confirmed.⁴³ The mechanism by which exposure to trichloramines can contribute to the development of allergic diseases, rhinitis, and/or airway hyperresponsiveness remain to be investigated. Further studies should focus on the contribution of NCl_3 to oxidative stress, epithelial damage, inflammation, and remodeling. The time course and efficiency of airway epithelial repair after inhalation of chlorine byproducts is also currently unknown in swimmers. Overall, the risks-benefits balance of swimming activities (particularly when repeated and intense) remains to be studied in people attending chlorinated swimming pools. Further study is needed to determine if healthy adult and child swimmers, both recreational and competitive, lifeguard attendants, and those with respiratory disorders are vulnerable to the effects of inhaled chlorinated byproducts.

More studies are needed on the optimal preventative measures and management of upper and lower airway disorders in swimmers and these measures need to be adequately implemented. A recent study showed that in swimmers complaining of rhinitis symptoms, the inflammation was mostly neutrophilic,⁴⁴ suggesting that ICS could have limited benefit in this condition. Anticholinergic drugs and/or regular nasal irrigation with a saline solution may be considered. Nutritional interventions, through supplementation with omega 3 or antioxidants, may reduce airway hyperresponsiveness in elite swimmers,⁴⁵ reduce mucus accumulation, epithelial hyperplasia, and airway hyperresponsiveness after exposure to chlorine, as shown in a recent animal study,⁴⁶ but their effects remain to be better documented in humans.

DOES THE EPITHELIUM REGULATE LEUKOCYTE ACTIVATION?

Although it is possible that the movement of water out of the airways during exercise challenge leads directly to the activation of leukocytes or sensory nerves in the airways, a more unifying concept is that movement of water in the airways initiates events within the epithelium causing activation of airway leukocytes. It is clear that water transport or the addition of an osmolar solution to the airways is sensed by the epithelium, leading to the passive movement of water from the epithelial cells to restore the airway surface liquid osmolarity and volume.^{47–49} These events maintain the osmolarity of airway surface liquid, but are also accompanied by cellular signaling events that lead to the release of cellular adenosine triphosphate (ATP) and adenosine, the activation of chloride channels, and an increase in intracellular calcium in the epithelium.⁴⁸

The connection between the epithelial response to water loss and the activation of airway leukocytes needs to be understood in much greater detail. One possibility is that the eicosanoid precursor arachidonic acid or an intermediate in the leukotriene synthetic pathway is released by the epithelium leading to production of eicosanoids that mediate bronchoconstriction via a transcellular metabolism.^{50,51} Another possibility is that the epithelium releases an enzyme that increases eicosanoid production in leukocytes.⁵² One candidate for this role is secreted phospholipase A_2 group X ($\text{sPLA}_2\text{-X}$), which is the predominant sPLA_2 in the airway epithelium⁵³; preliminary evidence indicates that $\text{sPLA}_2\text{-X}$ is released into the airways after exercise challenge in individuals with asthma.⁵⁴ The release of $\text{sPLA}_2\text{-X}$ by the epithelium may be important in the pathogenesis of EIB because leukocytes such as eosinophils are activated to release leukotrienes by this epithelial-derived enzyme.⁵⁵ As differentiated cultures of primary human airway epithelial cells in organotypic culture are now possible, much more work should be conducted on the epithelial response to water transfer and the nature of the products that are released by epithelial cells in response to this stimulus. The release of specific epithelial-derived products that are identified will need to

be examined using *in vivo* model systems of EIB. In this regard, animal models that can capitalize on the revolution in molecular immunology using genetically altered organisms should be further developed. A well-described murine model of EIB has not been developed although there is a well-described canine model of EIB.⁵⁶ Other species such as guinea pigs also develop hyperpnea-induced bronchoconstriction even in the absence of sensitization, but genetic alterations in these animals are not readily achieved at this time.

WHAT IS THE CONTRIBUTION OF THE SENSORY NERVES?

Sensory nerves in the airways may serve as a final common pathway leading to bronchoconstriction in EIB, but many of the specific details about this pathway remain unanswered. Early studies using inhaled lidocaine to prevent EIB did not support a role of sensory nerve afferent pathways^{57,58}; however, subsequent studies with neurokinin (NK)₁ receptor antagonists in human subjects suggested that there might be some efficacy in blocking this pathway.^{59,60} When activated, C-fibers from sensory nerves initiate the release of tachykinins via retrograde axonal transmission.^{61,62} C-fibers transmit this activation signal to goblet cells and airway smooth muscle, leading to goblet cell degranulation and mucus release.^{32,63} Sensory nerves are activated by eicosanoids, and the activation threshold for sensory nerves is decreased in the presence of leukotrienes.^{64,65} Other eicosanoids such as prostaglandin (PG)_{D2} that cause bronchoconstriction in humans could also act via sensory nerves, although PGD₂ can also have direct effects on airway smooth muscle via thromboxane receptors.⁶⁶ A major limitation to understanding this system in humans is that the predominant tachykinin in humans is NK A, which has high affinity for the NK₂ receptor; substance P is present in humans at lower levels and predominantly binds to the NK₁ receptor.^{67,68} As receptor antagonists become available for the 3 different NK receptors (ie, NK₁, NK₂, NK₃), a better understanding of the role of sensory nerves in EIB can be ascertained. The sensory nerve system may act as a target for eicosanoids in the airways and may initiate the activation of leukocytes that are in close proximity to airway nerves.

Sensory nerves are also stimulated by changes in osmolarity⁶⁹ and coughing is a common feature of hyperpnea with dry air and inhalation of hyperosmolar and hypo-osmolar aerosols.^{70,71} In studies of nasal challenge with hyperosmolar stimuli, there was a significant increase in 15-hydroxyeicosatetraenoic acid (15-HETE) in allergic but not healthy individuals.⁷² 15-HETE is derived from the epithelium⁷³ and is an endogenous ligand for the vanilloid receptor TRPV₁.

IS MAST CELL INFILTRATION OF THE EPITHELIUM IMPORTANT IN EIB?

Mast cells have long been postulated to play a central role in the pathogenesis of EIB, in part as a result of the effectiveness of cromones to prevent EIB and the responses to surrogates of exercise.^{35,74,75} Mast cell degranulation after exercise challenge has been specifically demonstrated in individuals with EIB.¹⁹ These findings have led to the presumption that mast cell infiltration of the airways may be a defining susceptibility feature of patients with EIB. Little work has been done, however, to characterize differences in mast cell populations in the airways or the potential regulation of such mast cell populations. A recent study identified an increase in the expression of trypsinase and carboxypeptidase A3 (CPA3) genes in the airway epithelium in asthma, particularly in the Th2 high molecular phenotype of asthma⁷⁶; further study found that the number of intraepithelial mast cells was increased in the Th2 high phenotype of asthma (Fig. 1).⁷⁷ As the development of mast cell granules and possibly mast cell

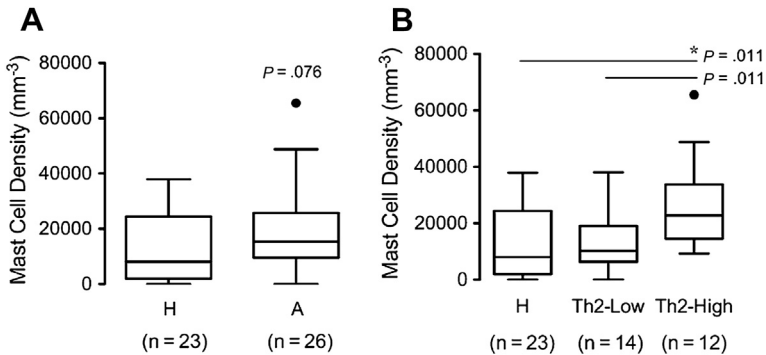


Fig. 1. Density of mast cells, within airway epithelium, among subjects stratified by disease status (A) and by Th2 subgroup (B). Lines represent median values and boxes represent interquartile ranges. A, asthmatic; H, healthy. * $P = .011$, Kruskal-Wallis test. (*Reproduced from* Dougherty RH, Sidhu SS, Raman K, et al. Accumulation of intraepithelial mast cells with a unique protease phenotype in T(H)2-high asthma. *J Allergy Clin Immunol* 2010;125:1046–53; with permission.)

function can be regulated in peripheral tissues, these findings are particularly notable as mucosal mast cells typically do not express CPA3.⁷⁸ A study comparing airway cell gene expression obtained by induced sputum found that both tryptase and CPA3 genes were among the most differentially overexpressed in asthmatics with EIB relative to asthmatics without EIB, especially after exercise challenge.⁷⁹ More studies are needed in this area to delineate the mast cell population in the airway epithelium and airway wall of patients with EIB, and the regulation of such mast cell populations by the airway epithelium.

WHAT IS THE ROLE OF LIPID MEDIATORS?

Several lines of evidence demonstrate the overproduction of certain inflammatory eicosanoids such as the cysteinyl leukotrienes (CysLTs) and PGD₂ in patients with EIB. Mast cells are the major source of PGD₂. A significant increase in the urinary excretion of 11 β -PGF_{2 α} , a metabolite of PGD₂, has been observed after exercise,⁸⁰ eucapnic voluntary hyperpnea with dry air,^{81,82} and inhaled mannitol, which serves as a surrogate for exercise challenge.⁷⁵ An important unanswered question is whether PGD₂ plays a causal role in the development of EIB. The increase in PGD₂ is related to the % decrease in forced expiratory volume in the first second of expiration (FEV₁) after eucapnic voluntary hyperpnea (Fig. 2).⁸¹ Further drugs that attenuate EIB, including sodium cromoglycate^{75,81} and beclomethasone,⁸² prevent the increase in PGD₂ after challenge (Fig. 3).^{81–83} In response to mannitol, there is a relationship between the change in urinary levels of 11 β -PGF_{2 α} and the change in leukotriene (LT)E₄,⁸⁴ suggesting that LTE₄ is also likely to be released from mast cells or that the release occurs in parallel (Fig. 4). Whether this same relationship occurs in response to exercise in those with or without sputum eosinophilia is not known. Eosinophils are a potential source of CysLTs. Studies have also reported an increase in the urinary concentration of both 11 β -PGF_{2 α} and LTE₄ after challenge with mannitol and exercise in nonasthmatics without airway hyperresponsiveness.^{85–87}

Lipid mediators such as CysLTs and PGD₂ are eicosanoids that are derived from arachidonic acid.⁸⁸ There are also protective lipid mediators that are derived from

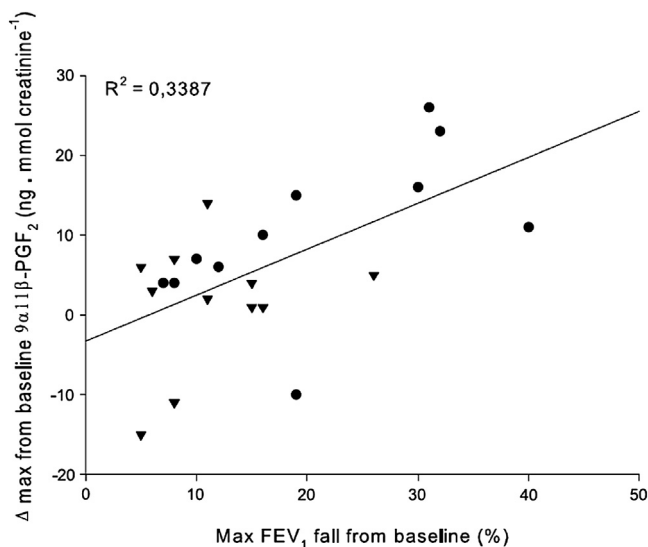


Fig. 2. Correlation between the degree of bronchoconstriction after eucapnic voluntary hyperpnea and excretion of urinary 9α,11β-PGF₂ in athletes with EIB after administration of placebo (circles) or 40 mg of sodium cromoglycate (triangles). (Reproduced from Kippelen P, Larsson J, Anderson SD, et al. Effect of sodium cromoglycate on mast cell mediators during hyperpnea in athletes. *Med Sci Sports Exerc* 2010;42:1853–60; with permission.)

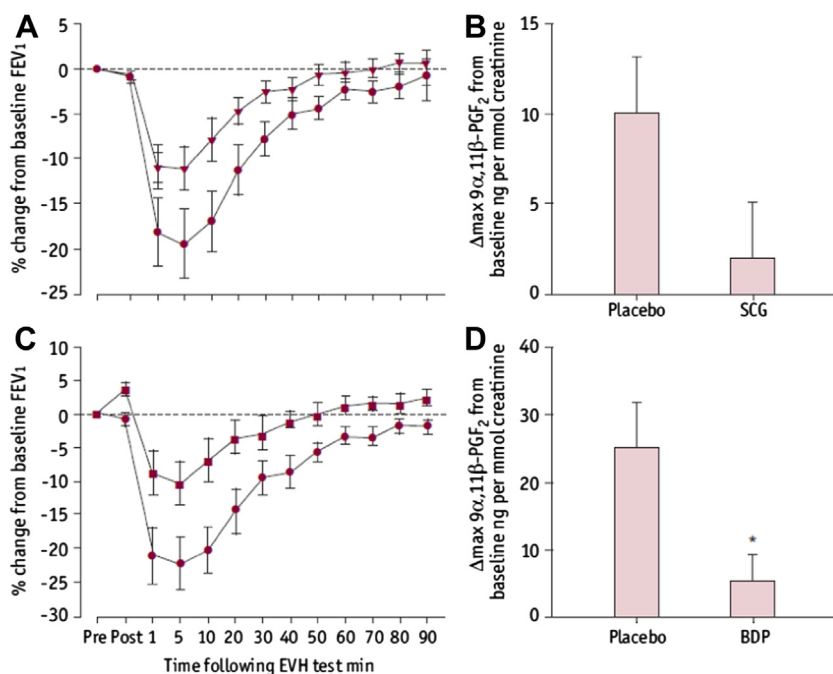


Fig. 3. (A, C) The percentage change in FEV₁ from baseline and (B, D) maximum change in 9α,11β-PGF₂ in response to 6 minutes of eucapnic voluntary hyperpnea (EVH) with dry air (A, B) in the presence of placebo (closed circles) and after sodium cromoglycate (inverted triangles) in 11 subjects with greater than 10% decrease in FEV₁ and (C, D) 4.5 hours after placebo (closed circles) and 1500 μg of beclomethasone (squares) in 8 subjects with asthma. (Reproduced from Anderson SD, Kippelen P. Stimulus and mechanism of exercise-induced bronchoconstriction. *Breathe* 2010;7:25–33; with permission.)

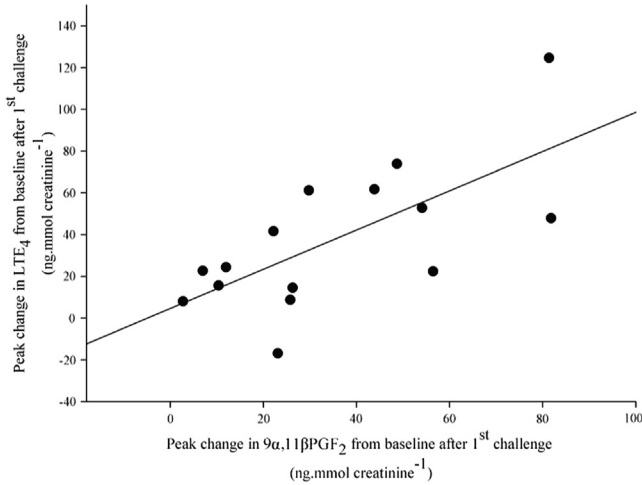


Fig. 4. Correlation between the peak concentration of LTE₄ and 9α,11β-PGF₂ after a mannitol challenge. $r = 0.686$, $P < .005$, $n = 15$. (Reproduced from Larsson J, Perry CP, Anderson SD, et al. The occurrence of refractoriness and mast cell mediator release following mannitol-induced bronchoconstriction. *J Appl Physiol* 2011;110:1029–35; with permission.)

the same arachidonic acid precursor and a range of other protective mediators that are derived from the metabolism of related free fatty acids other than arachidonic acid.⁸⁹ The regulation of eicosanoid formation is complex, can involve transcellular metabolism, and is often dictated by the terminal synthetic enzyme within a cell. One study found that the levels of the protective lipid mediator lipoxin A₄ decreased after exercise challenge and that the levels were lower in asthmatics with EIB relative to asthmatics without EIB.⁹⁰ Another mediator in the airways that decreases after exercise challenge in individuals with EIB but not normal individuals is PGE₂.¹¹ One possibility is that the reduction in the production of these mediators (ie, PGE₂ and LXA₄) represents epithelial dysfunction in asthma. Epithelial cells treated with interleukin (IL)-13 *in vitro* have reduced capacity for PGE₂ synthesis through a reduction in the synthetic enzymes cyclooxygenase-2 (COX-2) and PGE synthase 1.⁹¹ Epithelial cells normally have an inhibitory effect on mast cell activation, but this protective effect is reduced in epithelial cells derived from individuals with asthma, suggesting that a regulator of mast cell activation is reduced in people with EIB.⁹² It is known that inhaled PGE₂ inhibits EIB⁹³ and that PGE₂ directly alters CysLT formation in cultured mast cells.⁹⁴ More studies are needed to refine our understanding of eicosanoid metabolism in patients with EIB, and particularly the loss of protective mediators related to alterations in the airway epithelium in asthma.

WHAT IS THE ROLE OF RELEASED MEDIATORS AND THE DEVELOPMENT OF REFRACTORINESS?

Refractoriness is defined as a decrease in the airway response to repeated challenge with the same stimulus within 2 to 4 hours of the initial stimulus. A decrease in release of mediators of bronchoconstriction on repeated challenge was proposed as a possible mechanism,⁹⁵ but subsequent studies have not supported this hypothesis.^{84,96} Because of the inhibitory effect of indomethacin on refractoriness, PGE₂ has

been suggested to play a vital role^{97–101} although no studies have confirmed this directly.

Conflicting results have been documented when the first challenge is performed breathing hot humid air and the second challenge breathing dry air, and this needs further investigation. Three studies found protection from dry air challenge after an initial exercise challenge while inhaling hot humid air.^{102–104} This protection was abolished by indomethacin. In complete contrast, 2 other investigators reported severe EIB after breathing dry room air 20 minutes after an initial exercise breathing hot humid air (Fig. 5).^{105,106}

Although the occurrence of refractoriness after repeated challenge with exercise or surrogates of exercise may be dependent on mediator release, the occurrence of a protective effect after exercise challenge with humid air, in the absence of EIB, seems at odds with other results. Research is needed to investigate possible common links between the challenges; adenosine is one possible link. The change in airway surface liquid volume that may be expected to occur during challenge by exercise, eucapnic voluntary hyperpnea, distilled water, hypertonic saline, and mannitol is likely to lead to ATP release.⁴⁸ The ATP released can then be converted to adenosine and exert effects via the A_{2b} receptor to maintain the airway surface liquid volume.⁴⁸ The A_{2b} receptor is also the receptor on mast cells that causes mediator release when stimulated by adenosine.¹⁰⁷ Adenosine has been measured in expired breath condensate during EIB and there was a significant relationship between the increase in concentration of adenosine and the percent decrease in FEV_1 .¹⁰⁸

Many of the early studies in the 1980s and early 1990s focused on the pulmonary response with little interest in the molecular mechanisms underlying the refractory period. It is now well established that the release of mediators is involved in EIB,

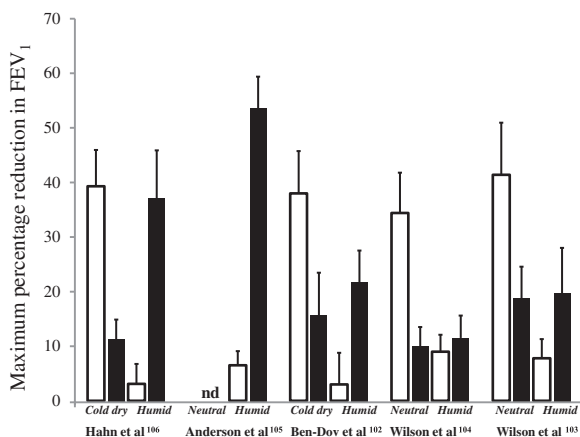


Fig. 5. Maximum percentage decrease in FEV_1 (mean ± SD) after exercise compared with values before exercise. The first challenge (*open bars*) was performed breathing either dry air (cold or room temperature) or humid air; the second challenge (*closed bars*) was always performed breathing dry air. Refractoriness was seen in all studies when the first challenge was performed breathing dry air but not with humid air. In the studies by Hahn and colleagues¹⁰⁶ and Anderson and colleagues,¹⁰⁵ no protective effect was seen during the second challenge when hot humid air was inspired during the first challenge. However, in the other studies by Ben Dov and colleagues¹⁰² and by Wilson and colleagues,^{103,104} a protective effect was seen during the second challenge when the first challenge was performed breathing humid air. The values are reproduced from the original data given.

and the technology available to measure biological pathways has improved. There is now greater availability of specific inhibitors of mediator synthesis as well as specific agonists and antagonists of the respective receptors for each mediator. These agents may reveal the specific mediators, in addition to CysLTs, that contribute to bronchoconstriction in EIB. For example, the evidence for the involvement of PGs is based on the effect of non-specific COX inhibitors, which indicates a role for PGE₂; however, no further conclusion can be drawn. When studying the effects of different drugs not only the pulmonary response but also mediator release needs to be taken into consideration. Similarly some PGD₂ antagonists have been shown to provide no benefit against EIB.¹⁰⁹ More specific antagonists to a wider range of receptors for PGD₂ and its metabolites may become available and need to be tested.

Another great advantage is the development of increasingly sensitive and specific methods for measuring the various mediators. The possibility of performing metabolomics will be a great help in the search for new mediators and in understanding the relationship between the currently known mediators. Until now, much of our knowledge on the mechanism of EIB was based on the levels of LTE₄ and the PGD₂ metabolite 11 β -PGF_{2 α} .^{80–82,110} Using lipidomics, it will be possible to study several mediators and their metabolites simultaneously in the same sample, and compare patterns of release and their dynamics. The ability to measure mediators in different media (eg, sputum, saliva, urine, blood) before, during, and after challenge will also help to increase our understanding of the mechanism of EIB.

Additional studies are needed to investigate the reproducibility of the refractory period. It will be important to understand if variability in the refractory period among individuals is related to airway smooth muscle sensitivity, revealing a phenotype of the airway smooth muscle or other factors such as the intensity of cellular inflammation. A recent proposal that remains to be proved is that the high levels of CysLTs lead to desensitization of the CysLT receptor.⁸⁴

IS MILD EIB A DIFFERENT PHENOTYPE?

There are several observations that suggest that mild EIB may be a different phenotype than moderate or severe EIB. Mild EIB can be considered as less than 15% decrease in FEV₁ after exercise and possibly less than 20% decrease in FEV₁ in those with a normal percentage predicted value before exercise. Mild EIB is commonly observed in athletes and people with symptoms of asthma but without a formal asthma diagnosis.¹¹¹ Mild EIB is variable from day to day¹¹² and may benefit from dietary^{86,113–116} and environmental influences.^{117,118} Unlike moderate to severe EIB, mild EIB may not necessarily be associated with atopy,¹¹¹ an abnormal fractional concentration of nitric oxide in expired gas,¹¹⁹ or the presence of sputum eosinophilia.¹²⁰ Mild EIB may occur in cold-weather athletes suggesting that the vasculature may be contributing to airway narrowing.¹²¹ Inhaled β_2 agonists are effective in mild EIB but daily treatment with β_2 agonists results in loss in the duration of protection, slower recovery from EIB, and sometimes an increase in the severity of EIB.^{122–125} Daily treatment with ICS is effective against mild to severe EIB although low doses of ICS may not be as effective as high doses of ICS.¹²⁶ Drugs such as sodium cromoglycate or nedocromil sodium⁷⁴ and montelukast acutely inhibit mild to severe EIB¹²⁷ but not everyone is protected to the same extent. One important question is whether to treat mild EIB without symptoms, or treat mild EIB with symptoms with an inhaled β_2 agonist alone when required. It will also be important to understand the factors that lead to the progression of EIB severity in some individuals and if this can be prevented by early treatment.

WHAT IS THE BENEFIT OF LONG-TERM ICS ON EIB IN PERSONS WITH ASTHMA?

Few studies have investigated the treatment of EIB using regular ICS beyond a period of 12 weeks¹²⁸; many studies have focused on the benefits soon after introducing an ICS.¹²⁶ If the airway response to exercise and other indirect tests demonstrates a link between airway inflammation and a sensitive airway smooth muscle as previously proposed,¹²⁹ then resolution of EIB after ICS suggests the link between these 2 key features of asthma has been abolished with treatment. It is likely that both eosinophils and mast cells are sensitive to corticosteroid treatment and that mast cells may take longer to respond to treatment than eosinophils. An important question is whether the resolution of EIB in a person with asthma is a reliable objective marker of clinical control. Similarly, it will be important to examine the benefit of ICS in athletes who have EIB and asthma, and those who have EIB alone.

IS THERE A ROLE FOR THE ANTICHOLINERGIC DRUGS?

There is evidence to suggest that vagal tone of the airway smooth muscle may play an important role in the susceptibility to EIB. The variable efficacy of anticholinergic drugs in EIB may be due to variations in cardiac vagal activity that have implied that vagal stimulation may be important.^{130,131} There are an increasing number of anticholinergic drugs that may help resolve this question and determine if this variability in response is due to the potency of the drug. To date, few studies, if any, have investigated the use of these stronger anticholinergic drugs on EIB.

WHY DO CHILDREN GET EIB MORE QUICKLY AND RECOVER MORE QUICKLY?

It has been shown that many asthmatic children with EIB can have breakthrough EIB (ie, the onset of bronchoconstriction *during* exercise) within minutes after the start of exercise.^{132,133} Breakthrough EIB is accompanied by a more severe decrease in pulmonary function after exercise, and therefore apparently a sign of uncontrolled asthma.¹³³ Moreover, breakthrough EIB is a frustrating symptom that may result in premature withdrawal of a child from play and sports. We need to know which medications are best for prevention of the phenomenon of breakthrough EIB. A suggested mechanism to account for breakthrough EIB is an imbalance between bronchoconstrictor mediators (probably mast cell in origin) and bronchodilator PGs (probably epithelial in origin). The early breakthrough EIB observed in children compared with adults may be caused by differences in the proximity of the mast cells to the airway surface and their density, and the ability of the epithelium to produce PGE₂. In children, there is a shorter time to maximal bronchoconstriction and quicker recovery from EIB than has been described in adults.^{134–136} The time course of bronchoconstriction after exercise is age related and the younger the child, the shorter the time to maximal bronchoconstriction after exercise (Fig. 6).¹³⁴ The mechanism responsible for this difference between children and adults is unknown but may relate to differences in the epithelium or the site of mast cells. For example, a faster change in osmolarity may occur in children compared with adults, which may result in a more rapid onset of mediator release. It is unknown whether this cascade indeed happens faster at younger age.

The quick onset and recovery of EIB in young children could also be the result of a shortened response and relaxation time of the airway smooth muscle in airways of younger children. The age-related response of airway smooth muscle may partially be due to airway remodeling and a change in airway geometry with older age. Deep inspirations, as happen at the start of exercise, usually have a

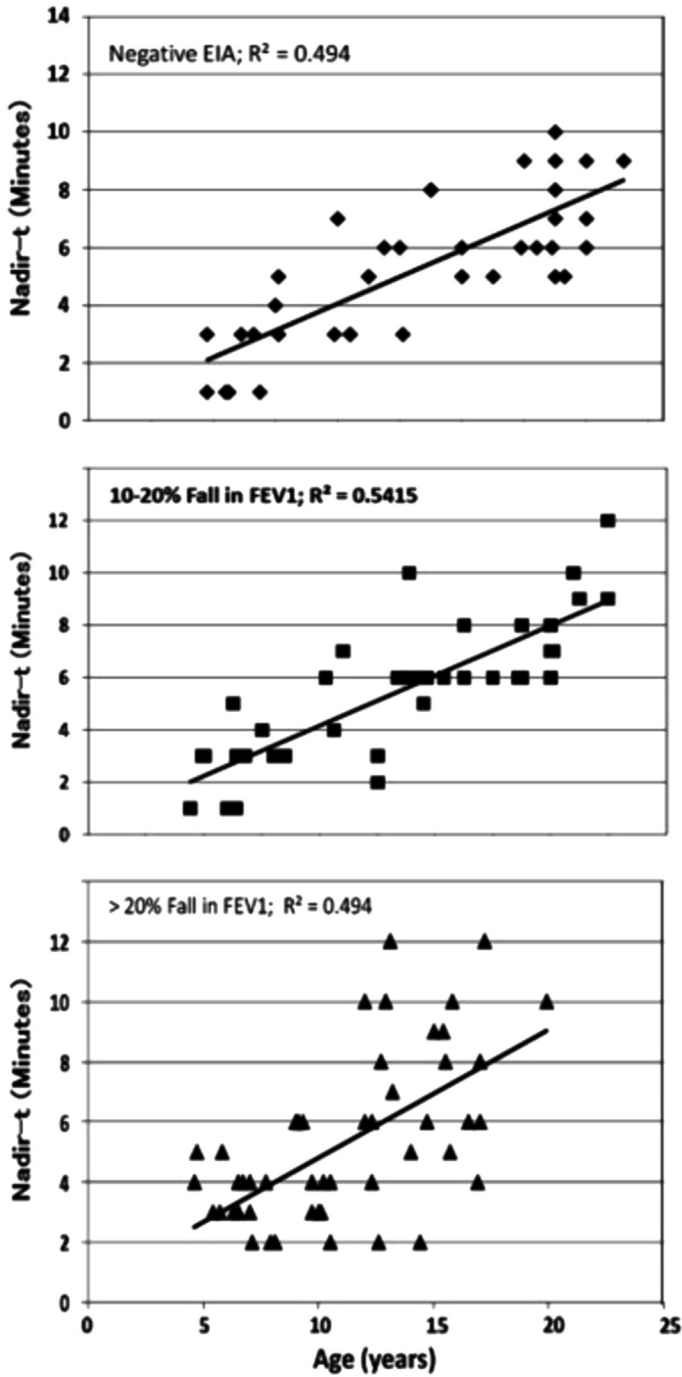


Fig. 6. The correlation between age and time to Nadir (Nadir-t). Data are divided according to potential cutoffs or a negative test. Each sign represents a single participant. (*Reproduced from Vilozni D, Szeinberg A, Barak A, et al. The relation between age and time to maximal bronchoconstriction following exercise in children. Respir Med 2009;103:1456–60; with permission.*)

bronchodilating effect in asthmatic children and healthy adults,¹³⁷ which is believed to be caused by relaxation of the airway smooth muscle.¹³⁸ This potent bronchodilating mechanism may fail in remodeled airways of adult asthmatics, as if the airway smooth muscle has become frozen and fails to fluidize.¹³⁸ Remodeling of the airways in asthmatic adults may hinder stretch-induced relaxation of smooth muscle and prevent the rapid onset of bronchoconstriction caused by stiffening of the airway smooth muscle cytoskeleton.¹³⁸ There is a lack of longitudinal studies on the evolution of EIB and breakthrough EIB from young asthmatic children into adulthood.

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