# Role of Cells and Mediators in Exercise-Induced Bronchoconstriction

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**KEYWORDS**

• Asthma • Eicosanoid • Eosinophil • Exercise-induced bronchoconstriction • Leukotriene • Mast cell • Phospholipase • Prostaglandin

**KEY POINTS**

- Patients who are susceptible to exercise-induced bronchoconstriction have epithelial shedding, infiltration of the airways with mast cells and eosinophils, and increased production of inflammatory mediators such as leukotrienes.
- During exercise and hyperpnea the inspired air is equilibrated to the conditions of the lower airways, resulting in the transfer of water out of the airways.
- Following exercise challenge, mediators such as cysteinyl leukotrienes and prostaglandin $D_2$ are released into the airways from mast cells and eosinophils.
- Sensory nerves may mediate the effects of cysteinyl leukotrienes and other lipid mediators, leading to smooth-muscle contraction and mucus release.
- The epithelium may serve as a regulator of leukocyte activation in response to water loss or osmotic stress, but the mechanism remains incompletely understood.

## INTRODUCTION

The role of inflammatory mediators in the pathogenesis of exercise-induced bronchoconstriction (EIB) has become increasingly clear from studies conducted in human subjects with asthma over the last 15 years. These results indicate very clearly that

Funding: Supported by National Institutes of Health grant HL089215.
Disclosures: T.S. Hallstrand has received research grants from the NIH, American Lung Association, has served as a consultant for Amgen and TEVA pharmaceuticals, and has received lecture fees from Merck & Co. W.R. Henderson has served on advisory boards for Gilead Sciences, has received lecture fees from Merck & Co., and has received industry-sponsored grants from Genentech and Gilead Sciences. W.A. Altemeier and M.L. Aitken have no conflicts of interest.
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Immunol Allergy Clin N Am 33 (2013) 313–328
http://dx.doi.org/10.1016/j.iac.2013.02.003 **immunology.theclinics.com**
0889-8561/13/$ – see front matter 

mediators from mast cells and other airway leukocytes are released into the airways following exercise challenge in individuals who are susceptible to EIB. The evidence that the release of such mediators plays a causal role in the pathogenesis of EIB is strongest for the cysteinyl leukotrienes (CysLTs) $C_4$, $D_4$, and $E_4$, in part because of the availability of receptor antagonists and synthesis inhibitors that alter the leukotriene (LT) pathway. It is also apparent that several other mediators that may play important roles in the pathogenesis of EIB are released into the airways, but the precise roles of these mediators are inferred from animal studies and from the basic biological function of the mediators. Many unanswered questions remain, including why leukocytes become activated in the airways, how either evaporative water loss or the addition of a hyperosmolar solution to the airways initiates downstream cellular effects, and what the connection is between the epithelium and these events that leads to leukocyte activation.

## ALTERATIONS IN THE AIRWAYS THAT LEAD TO EIB

As a prototypical feature of indirect airway hyperresponsiveness (AHR), EIB shares common features with other stimuli such as hypertonic aerosols and adenosine, which cause bronchoconstriction through the release of mediators.[1] EIB is only weakly related to structural alterations of the lung[2–4] and airway smooth-muscle hyperresponsiveness measured by direct-acting agonists of smooth-muscle contraction such as methacholine.[5] In one study of 27 asthmatic children, there was no relationship between the methacholine $PC_{20}$ and maximum decrease in forced expiratory volume in 1 second ($FEV_1$) after exercise ($r = -0.2$, $P = .40$). Another study of elite athletes found that 9 of 25 elite athletes with a positive eucapnic voluntary hyperpnea (EVH) challenge, a surrogate for exercise challenge, had a positive methacholine challenge, demonstrating the discordance between these 2 different features of AHR.[6] Collectively, these studies indicate that EIB is pathophysiologically distinct from other features of asthma, but shares common features with other forms of indirect AHR. A clear understanding of the pathophysiology of EIB is important, as EIB at an early age is associated with the persistence of asthma later in life.[7–9] There is also evidence that chronic lung disease early in life is a risk factor for the development or persistence of EIB later in life.[10]

As subjects with asthma can be characterized based on the presence or absence of EIB using a dry air exercise challenge test, several studies have made comparisons between asthmatics with and without EIB to better understand the basis for EIB. An inflammatory basis of EIB is suggested by an increase in the fraction of exhaled nitric oxide ($F_{ENO}$) among asthmatics who are susceptible to EIB,[11] especially in subjects with atopy.[12] Although differences in the concentration of inflammatory lipid mediators have not been identified in studies evaluating metabolites in the urine,[13] the concentrations of inflammatory lipid mediators are increased in the airways of individuals with EIB.[2,4,14] In particular, the concentration of CysLTs is increased in induced sputum of adults with EIB,[4] and in exhaled breath condensate (EBC) of children with EIB.[2] In addition, the levels of 8-isoprostanes, nonenzymatic products of phospholipid oxidation, are increased in EBC of asthmatics with EIB, and correlate with the severity of EIB.[14] There is also evidence of a reduction in the formation of protective lipid mediators in the airways such as lipoxin A4 in patients with EIB.[15] Prostaglandin $E_2$ ($PGE_2$) is a key regulatory eicosanoid that inhibits EIB when administered by inhalation.[16] The production of $PGE_2$ relative to CysLTs is reduced in patients with EIB.[4] As the epithelium is a major source of $PGE_2$, it is notable that the number of epithelial cells shed into the induced sputum is greater in patients with EIB.[4]