Exercise-induced bronchoconstriction (EIB) is the term used to describe the transient narrowing of the lower airways that follows vigorous exercise. Although EIB most commonly occurs in individuals with clinically recognized asthma, this condition is also reported in school children, armed forces recruits and elite athletes without asthma. Patients typically present with respiratory symptoms that are related to vigorous exercise. However, symptoms are poor predictors of EIB and should not be relied on for diagnosis.

Epidemiologic Characteristics
It is estimated that at least 80% of patients given a clinical diagnosis of asthma will have EIB at some stage of the disease process. Exercise-induced bronchoconstriction is among the first symptoms of asthma to appear, and it is typically the last symptom to disappear with treatment. Even after treatment with inhaled corticosteroids (ICSs), EIB can be demonstrated in a substantial proportion of patients with asthma.

Studies of EIB have been conducted with various cohorts in several countries. Surveys conducted 10 years apart (1993 and 2003) in Ghana showed an increase in prevalence of EIB in “urban rich” (4.2% to 8.3%), “urban poor” (1.4% to 3.0%), and rural (2.2% to 3.9%) children aged 9 to 16 years. In a study in Wales over a period of 30 years, the prevalence of EIB was reported to increase between 1973 and 1988 but decrease between 1988 and 2003 in the same geographical area. In a study of 802 school children in Australia, 157, or 19.6% of the children had EIB (defined as a decrease in FEV$_1$ ≥ 15%), and 40% of this group had no previous diagnosis of asthma.

Studies of athletes competing in the Olympic Games have provided useful data on asthma and EIB. There is a high prevalence of asthma among endurance Olympic athletes, both in winter sports (eg, cross-country skiing [17.6%], speed skating [16.2%]) and in summer sports (eg, cycling [15.3%], swimming [11.3%], modern pentathlon [10.1%]).

Another sporting group for whom a diagnosis of EIB is important is scuba divers. Breathing dry air from a tank while swimming underwater or at the surface is a stimulus for EIB. In a laboratory analysis of 180 intending divers who had a history of asthma but no recent symptoms and who were currently taking no medications and were otherwise medically fit to dive, 17% had a 15% decrease in FEV$_1$ from baseline, in response to inhaling an aerosol of 4.5% saline. Results suggested that their asthma was currently active.

Pathophysiologic Mechanisms
The physiologic stimulus for EIB is the loss of water, by evaporation, from the airway surface while conditioning large volumes of air in a short time. This water loss can result in airway cooling and dehydration of the airway surface. When exercise is performed with the inhalation of hot humid air, there is a marked reduction or complete inhibition of EIB. There are two hypotheses as to how water loss causes the airways to narrow—the thermal hypothesis and the osmotic hypothesis.

According to the thermal hypothesis, EIB is a vascular event involving vasoconstriction resulting from airway cooling during exercise, followed by a reactive hyperemia when the airways re-warm on stopping exercise. This hypothesis does not implicate either bronchial smooth muscle or release of mediators in the mechanisms of EIB.

According to the osmotic hypothesis, an increase in osmolarity of the
Airway Injury

A recent hypothesis proposes that airway injury plays an important role in the development of EIB and bronchial hyperresponsiveness in elite athletes. According to this hypothesis, as the smaller airways are recruited into the air conditioning process, there is an increased risk of dehydration injury to the airway epithelium. Plasma exudation occurs during restoration of the epithelium. It is proposed that as the airway smooth muscle becomes repeatedly exposed to plasma-derived products, the contractile properties of the muscle change, rendering it more sensitive. This process may result in hyperresponsiveness to such agents as methacholine or it may result in EIB (Figure 1).30,31

This type of airway injury may account for the high levels of hyperresponsiveness reported in endurance athletes, particularly those performing in cold climates and in swimming pools. Infections may also play a role in airway injury and development of hyperresponsive airways. To reduce the potential for airway injury and sensitization, athletes may be well advised to cease training in environments in which allergen or irritant levels are high.

Mediator Release

The mediators of EIB include prostaquinol D2 (PGD2), leukotrienes, and histamine. Histamine and PGD2 are important in determining the severity of the decrease in FEV1 and leukotrienes are important in sustaining this decrease. Indirect evidence supporting the role of these mediators includes the modifying effects of specific antagonists and cyclooxygenase inhibitors on EIB. Direct evidence implicating these mediators comes from studies reporting an increase in concentration in arteriosol plasma, induced spumum, and urine following exercise.40

There is an increase in urinary excretion of the major metabolite of PGD2 and the cysteinyl leukotriene LTC4 after hyperpnea with dry air. An increase in concentration of histamine, tryptase, and cysteinyl leukotrienes in spumum and an increase in histamine in arteriosol plasma have also been reported after exercise.1,40

Investigating EIB

Investigating EIB in the laboratory can be challenging, with a low yield of positive test results. Among the many reasons for this difficulty, the type of protocol used is the most important. Exercise at a suboptimal intensity or duration or a high water content of the inspired air (>10 mgs H2O per liter equivalent to 23°C and 50% humidity) can explain many false negative test results. The exercise required to provoke EIB is vigorous, consisting of 6 minutes (in children) to 8 minutes (in adults) of activity at 85% to 95% maximum heart rate—or a respiratory minute volume ventilation at least 17.5 times FEV1 and preferably more than 21 times FEV1. Running is preferable to cycling, because ventilation increases more rapidly with running. A source of dry air is required to ensure low water content of the air inspired during exercise. For some individuals, the inspired air may need to be cooled to provoke symptoms.

Even when accounting for all these factors, there is a natural variability in the airway response to exercise such that a single negative test result may not be sufficient to exclude the diagnosis of EIB. This variability is particularly relevant in patients with symptoms but without a definite diagnosis of asthma. Twenty-five percent of such patients may have 1 negative and 1 positive test result when exercise is performed under the same conditions within a few days. Natural variability also occurs in patients with definite asthma diagnoses. In patients with asthma, exposure to allergens and irritants can transiently enhance severity of EIB, and removal from allergens and irritants can reduce severity of EIB.

Surrogates of Exercise

The variables affecting response to exercise have led to the use of surrogates of exercise to identify EIB. The eucapnic voluntary hyperpnea (EVH) test is 1 such surrogate of exercise. The EVH test was developed and standardized in the 1980s to assess armed forces recruits for EIB. For the test participant to maintain eucapnia (ie, normal carbon dioxide level), the EVH test requires inhaling a dry gas mixture containing 4.9% to 5.0% carbon dioxide, 21% oxygen, and balance nitrogen. The protocol requires hyperventilating the dry gas mixture for 6 minutes at 30 times FEV1.

The test is based on the principle that for most individuals, the maximum level of ventilation achieved during exercise is 17 to 21 times FEV1—well below the ventilation achieved by voluntarily hyperventilating (ie, about 30 times FEV1). Thus, the high ventilation rate and the dry air result in a low rate of false negative test results for EIB.

The EVH test has been used to assess large numbers of elite athletes for EIB. A study conducted in the United King-
dom demonstrated that the EVH test could identify EIB in previously undiagnosed elite athletes. Further, for many athletes the clinical diagnosis of EIB was not confirmed by the test result. 47

Some disadvantages exist in performing exercise and EVH evaluations with dry air. Breathing dry air at high flow volume can give some individuals a sore throat. At high flow, the resistance of the breathing circuit must be very low if patients are to easily achieve their maximum ventilation. Finally, both the exercise and EVH tests use a maximum bolus stimulus and, as such, severe decreases in FEV\textsubscript{1} (>30% from baseline) often occur.

**Mannitol Dry Powder Challenge**

In order to avoid excessive declines in FEV\textsubscript{1}, a test with mannitol can be used to identify the potential for EIB that is provoked by an increase in airway osmolarity and mediator release. The mannitol dry powder challenge requires the participant to inhale increasing doses of a dry powder of mannitol to a cumulative dose of 635 mg, with FEV\textsubscript{1} measured 60 seconds after each dose. 49,50 The mannitol test kit includes prepacked capsules and an inhaler device (Aridol; Pharmaxis Inc, Exton, Pennsylvania). A positive response to mannitol is indicated by a 15% decrease in FEV\textsubscript{1}, a value that represents the 95% confidence interval observed in healthy individuals without

**Figure 1.** Flow chart describing the pathophysiologic events leading to exercise-induced bronchoconstriction (EIB) in a classic case of a patient with asthma (left) and the pathophysiologic events leading to the development of bronchial hyperresponsiveness and EIB in an athlete (right). Abbreviations: AHR, airway hyperreactivity; Ca, calcium; Cl, chlorine; FEV\textsubscript{1}, forced expiratory volume in 1 second; K, potassium; Na, sodium; PGE\textsubscript{2}, prostaglandin E\textsubscript{2}. Reproduced with permission from Anderson and Kippelen. 30

![Flow chart](image-url)
asthma. The target of a 15% decrease from baseline FEV$_1$ results in fewer FEV$_1$ falls of more than 30% compared with exercise and EVH. 50

The index used to assess sensitivity to mannitol is the provoking dose to cause a 15% decline in FEV$_1$ (ie, PD$_{15}$). The index used to express reactivity or rate of change is the response dose ratio (RDR). The RDR is calculated by dividing the final percentage decline in FEV$_1$ by the dose of mannitol (in mg) that provoked that decline. 49 The PD$_{15}$ and RDR values to mannitol have been compared with patient responses to exercise and to EVH. The repeatability of the PD$_{15}$ measure of bronchial responsiveness to mannitol was found to be 1.1 doubling doses in a cohort of children with asthma. 51

Although a positive response to the mannitol challenge is the provoking dose to cause a 15% decline in FEV$_1$ (ie, PD$_{15}$). The index used to express reactivity or rate of change is the response dose ratio (RDR). The RDR is calculated by dividing the final percentage decline in FEV$_1$ by the dose of mannitol (in mg) that provoked that decline. 49 The PD$_{15}$ and RDR values to mannitol have been compared with patient responses to exercise and to EVH.

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Although a positive response to the mannitol challenge is more likely in patients who are atopic, there have been many positive test results recorded in individuals without atopy to common allergens.

A positive response to the mannitol challenge reveals the potential for EIB, and in individuals with a clinical diagnosis of asthma, the PD$_{15}$ and RDR values are indirect indices of EIB severity. 52, 53 A 10% decrease in FEV$_1$ has been used by some investigators to compare patient response to mannitol with responses to EVH and exercise. 53, 56 In a study of patients with symptoms of asthma but no definitive diagnosis who had EIB identified on at least 1 of 2 identical exercise tests, a mannitol challenge performed in fewer than 35 minutes showed sensitivities of 64%, 75%, and 83% to identify exercise-related FEV$_1$ decreases of 10%, 15%, and 20%, respectively. 50 However, in the same study population, the frequency of a 15% decrease in FEV$_1$ in response to mannitol was 1.65 times that of a 15% decrease in FEV$_1$ from exercise (when only the first of 2 identical exercise tests was considered). 50

**Prevention**

Prevention of EIB can be achieved on a short-term basis in the majority of patients with use of an inhaled β2-agonist (IBA), either short-acting or long-acting, immediately before exercise. 57-59 The IBA inhibits EIB by stimulating the β2 receptors at 2 sites. Stimulation of 1 site, on the mast cell surface, prevents release of mediators. Stimulation of the other site, on the bronchial smooth muscle, inhibits contraction by such agonists as histamine, leukotrienes, and PGD$_2$.

The use of IBAs does not address the underlying inflammation that leads to EIB, and there are a number of limitations in relying solely on these drugs. 60, 61 For example, daily use of any IBA leads to tolerance to its benefits, both at the mast cell and the bronchial smooth muscle. This tolerance has a rapid onset, usually within 1 week, and is unaffected by concomitant use of ICS.

Tolerance can manifest itself in several ways. First, a reduction in the duration of protection can occur, such that a short-acting IBA may protect for only 2 hours against EIB, and a long-acting IBA may protect for only 4 to 6 hours. 61 Second, after an attack of asthma provoked by exercise, the time to recover to baseline FEV$_1$ is prolonged. In addition, the IBA dose required for rescue is higher in patients taking IBAs on a daily basis. 62, 63 Finally, EIB has been reported as being more severe after introduction of an IBA on a daily basis. 64 Tolerance in EIB likely results from down-regulation of the β2 receptors, leading to a reduced number of receptors on the mast cell surface so that mediator release is no longer inhibited after a few hours. 65, 66

![Figure 2. Distribution of percentages of adult patients achieving various percentage decreases in forced expiratory volume in 1 second (FEV1) from preexercise baseline values after 8 weeks of treatment with montelukast or treatment with the inhaled β2-agonist salmeterol. P=.028 for overall distribution of maximal percentage decrease at week 8 between montelukast group and salmeterol group. Exercise was performed 21.4 hours to 21.8 hours after montelukast (10 mg once daily) or 9.1 hours to 9.6 hours after salmeterol (50 mcg twice daily). Error bars denote the standard error of the mean.](image)
Drug tolerance (i.e., tachyphylaxis) is acknowledged in the clinical setting in that patients with asthma who use IBAs daily are usually advised by their physicians to take additional inhalations of their medication immediately before exercise. Although these additional doses can overcome the tolerance problem in the short term, they contribute to sustaining the state of tolerance. Importantly, tolerance does not develop with irregular, intermittent use of IBAs (e.g., 3 times a week). Full response to IBAs is usually restored after 72 hours of abstinence.67

There are other medications that can be effectively used to inhibit EIB, but they do not usually prevent EIB completely.57,68 These agents include leukotriene antagonists and 5-lipoxygenase inhibitors. The most commonly reported agent used to treat patients with EIB is montelukast, which is taken as a tablet and requires several hours before it becomes effective.69 An advantage of montelukast over IBAs (e.g., salmeterol) is that tolerance to the protective effect does not occur with daily use, and the duration of protection remains as long as 24 hours (Figure 2).70,71 Furthermore, montelukast enhances recovery of FEV1 to baseline levels and reduces both the severity and length of the asthma attack after exercise. However, montelukast typically provides only about 60% protection against EIB—and not all users benefit to that extent.

Inconsistent findings have been reported with use of histamine antagonists.72,73 However, the combination of a histamine and a leukotriene antagonist has been found to inhibit the severity of the decrease in FEV1 and the time of the asthma attack after exercise.40

The mast cell stabilizing agents sodium cromoglycate and nedocromil sodium also inhibit EIB.74 The duration of the protective effects of these 2 medications against EIB is usually less than 3 hours. However, these agents have an immediate onset of action (allowing them to be inhaled just before the start of exercise), tolerance does not develop to these agents, and they do not need to be taken regularly. Their primary mode of action appears to be prevention of the release of PGD2 and reduction of the release of leukotrienes.41

There are nonpharmacologic methods of inhibiting or preventing EIB. For example, the 80% or more protection against EIB afforded by inspiring air conditioned to body temperature and fully saturated with water is greater than or equivalent to that provided by most medications in recommended doses.16,17,75-79 This method is not recommended as treatment, however, because the airways are a major means of reducing heat stress and maintaining normal body temperature. Nevertheless, this observation indicates that the EIB stimulus is close to the airway surface, emphasizing the importance of climatic conditions in determining EIB severity.

Some devices (e.g., masks and heat exchangers) permit a small amount of water vapor to be rebreathed during exercise. This small amount of water may be effective in preventing some cases of EIB, because it reduces the number of airway generations required to condition the inspired air.

An unusual but practical way of preventing EIB is to determine if the patient becomes refractory to repeated exercise. Many years ago—before the advent of effective medications—some athletes found that they could provoke their EIB and then recover before the game, allowing them to complete the
game free of EIB. The reason for this effect is not well understood, though recent evidence suggests that tolerance develops to the contractile effects of the mediators released in the initial bout of exercise. 75

**Treatment**

When EIB occurs, it responds rapidly to treatment with IBAs. 76 For the long-term resolution of EIB in both children and adults, treatment with ICSs is required. Inhaled corticosteroids such as budesonide, ciclesonide, and fluticasone have all been shown to reduce severity of EIB within 3 to 12 weeks. 16,17,77-79 The onset of protection achieved with ICSs is more rapid when higher doses are used (Figure 3). 78

The value of regular treatment with an ICS alone is that the majority of patients with EIB have normal spirometry values requiring a bronchodilator only before exercise. In patients with suboptimal spirometry values, combination of a long-acting IBA with an ICS has been shown to reduce severity of EIB. 16,17 In a pilot study, however, withdrawal from the long-acting IBA while remaining on the ICS demonstrated a reduction in the severity of EIB in children. 80

Because ICSs are so effective in long-term treatment of EIB, patients should verify, on a regular basis, whether they still have EIB and still need to take an IBA immediately before exercise. Such verification will help ensure that patients are not taking extra doses of IBAs unnecessarily.

Some dietary products, including fish oil, have been reported to provide protection against EIB. 81,82 It is important to note that the severity of EIB in such studies was mild, and individuals with moderate to severe EIB cannot rely solely on dietary methods of IEB control.

Finally, physical fitness plays a role in EIB occurrence. In individuals who are unfit, EIB will occur at a lower intensity of exercise. Some studies have examined improving physical fitness as a way of treating patients with EIB. 83,84

**Final Notes**

In summary, exercise-induced bronchoconstriction occurs in people with clinically recognized asthma and in elite athletes without other signs of asthma. EIB is a consequence of the thermal and osmotic effects of evaporative water loss in conditioning large volumes of air over a short period. Exercise testing is difficult to standardize and responses vary considerably over days. For this reason, surrogates of exercise such as eucapnic voluntary hyperpnea and dry powder mannitol, given by inhalation, are often used to identify potential for EIB. Mast cell mediators (eg prostaglandins, leukotrienes and histamine) and neuropeptides from sensory nerves are all likely to contribute to EIB. Exercise-induced bronchoconstriction is prevented in the short-term by inhaling a β2 agonist immediately before exercise, and in the long-term by regular treatment with inhaled corticosteroids. There are non-pharmacologic approaches to treating patients with EIB that include using face masks in cold weather and improving the physical fitness of those who are unfit.

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