



Exercise-Induced Asthma

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Exercise-induced asthma is a common disease affecting at least 15 million people in the United States. The etiology of exercise-induced asthma is not completely understood, although it is most probably triggered by cooling and dehumidifying of the respiratory airways during physical activity. Symptoms generally are related to bronchospasm and manifest 3-5 minutes after the physical activity ceases or 5-10 minutes into continued activity. Symptoms continue for approximately 10-30 minutes and are followed by a refractory period of 20-120 minutes. Exercise-induced asthma can be diagnosed using medication trials or by exercise challenge with peak-flow or spirometric monitoring. Treatment consists of controlling the underlying asthma; use of beta-adrenergic, mast cell inhibitor, or leukotriene antagonist medications; and by altering the ambient conditions under which the activity occurs. As a result, affected persons can live healthier lives and have better self-image.

Introduction

Exercise-induced asthma (EIA) is a common problem. A 1976 study¹ indicated that 63% of children with asthma and approximately 40% of atopic, nonasthmatic children had demonstrable EIA. About 15 million people in the United States are known to have EIA. In addition, 25% of children who have a decrease of >20% in peak expiratory flow rate (PEFR) with exercise never complain of symptoms; they simply stop participating in activities. This article reviews the pathophysiology, clinical presentation, diagnosis, and treatment of EIA.

Definition of EIA

Many definitions of asthma have been used over the years. The most recently revised definition issued by the NIH National Heart, Lung, and Blood Institute Expert Review Panel consisted of a lengthy paragraph which essentially underscored our lack of certainty about the fundamental cause of asthma.² For our

purposes, asthma can be defined as a chronic, inflammatory disease of the airways triggered by multiple stimuli, resulting in reversible bronchospasm, and characterized by repeated episodes of dyspnea, wheezing, chest tightness, cough, and phlegm. EIA can be defined as bouts of asthma (with bronchospasm the main component) triggered by exercise.

Pathophysiology of EIA

The manifestations of EIA offer some insight into possible causative mechanisms. In persons who have EIA, the first 3-5 minutes of physical activity usually have normal effects. When the physical activity stops, lung function decreases (as measured by PEFR or forced expiratory volume in one second, FEV₁) within the 5-10 minutes after the activity stops; if physical activity resumes, symptoms begin to manifest during the first 5-10 minutes of resumed activity. This decrease in pulmonary function is usually ac-

companied by symptoms and persists for 15-40 minutes; pulmonary function then normalizes, and symptoms resolve (Figure 1).³ Decreases in FEV₁ or PEFR often range from 20% to 50%. This early-phase response is the most common manifestation of EIA. In a few individuals, a late-phase response related more to inflammatory changes may occur within 3-10 hours after physical activity stops. The degree of late-phase decrease in pulmonary function is usually greater and more prolonged than in the early-phase response. A refractory period ranging from 40 minutes to 2 hours follows an episode of EIA; during this refractory period, it is difficult to recreate symptoms.

Multiple factors appear to affect frequency and severity of the change in pulmonary function and symptoms. To study possible pathologic pathways by which symptoms are produced, two primary models of asthma have been used: induction of symptoms by exercise and induction of symptoms by isocapnic hyperventilation. Use of these two models has led to the following information:

- The greater the person's baseline level of bronchial hyperreactivity as measured by histamine or methacholine challenge, the greater the likelihood of EIA developing or worsening.
- The greater the minute ventilation (with all other factors controlled), the greater the

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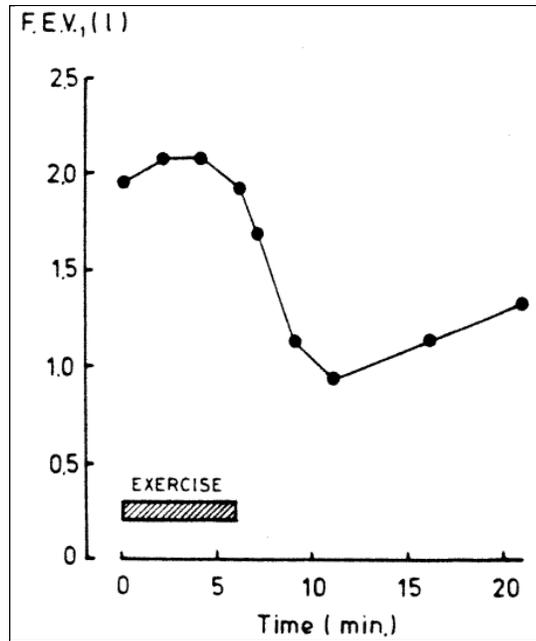


Figure 1. Typical pattern of lung function changes in response to minutes of running by an asthmatic child. (Adapted and reproduced by permission of the publisher from: Godfrey S. Exercise-induced asthma. In: Bierman CW, Pearlman DS, editors. Allergic diseases from infancy to adulthood. 2nd ed. Philadelphia: Saunders;1988. p.598.)

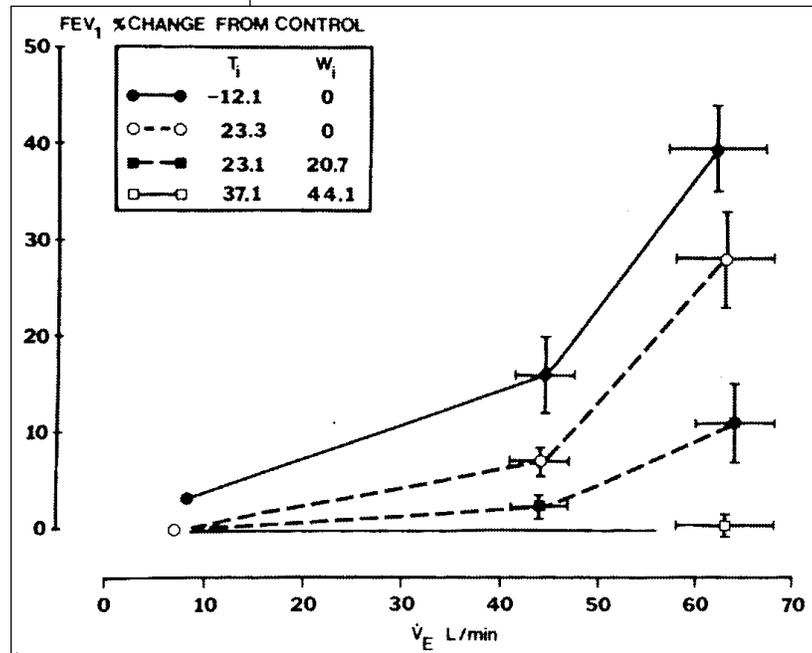


Figure 2. Comparison of changes that developed in 1-s forced expiratory volume (FEV_1) after exercise vs those observed after eucapnic hyperventilation in subjects breathing air at various temperatures and water contents.

(Figure created from data in: Deal EC Jr, McFadden ER Jr, Ingram RH Jr, Jaeger JJ. Hyperpnea and heat flux: initial reaction sequence in exercise-induced asthma. *J Appl Physiol* 1979;46:476-83 [p480(5)]; Deal EC Jr, McFadden ER Jr, Ingram RH Jr, Strauss RH, Jaeger JJ. Role of respiratory heat exchange in production of exercise-induced asthma. *J Appl Physiol* 1979;46:467-75(6); Strauss RH, McFadden ER Jr, Ingram RH Jr, Deal EC Jr, Jaeger JJ. Influence of heat and humidity on the airway obstruction induced by exercise in asthma. *J Clin Invest* 1978;61:433-40(7); Strauss RH, McFadden ER Jr, Ingram RH Jr, Jaeger JJ. Enhancement of exercise-induced asthma by cold air. *N Engl J Med* 1977;297:743-7(8).)

intensity and duration of EIA up to a maximum of two thirds of the individual's maximum working capacity.⁴

- The less humid the inspired air, the greater the trigger for EIA (Figure 2).⁵⁻⁸
- The cooler the air, the greater the trigger for EIA (Figure 2).⁵⁻⁸
- Exposure to airborne allergens worsens EIA.
- Certain air pollutants (eg, ozone) may worsen EIA.

This work and certain physiologic studies in animal models have led to two hypotheses of the pathway to EIA: one hypothesis focusing on water loss and another hypothesis focusing on postexertional rewarming of the airway.

The water-loss hypothesis (currently preferred) states that exercise causes decreased airway humidity through more rapid ventilation and thus increases mucosal osmolarity. Consequently, osmoreceptors trigger increased bronchial blood flow, which causes edema. Simultaneously, the increased osmolarity induces release of mediators that induce contraction of smooth muscle and additional obstruction of the airway. Slower production of inhibitory prostaglandins results in bronchodilation that ultimately reverses the smooth muscle contraction and manifests as the refractory period (Figure 3).⁹

This hypothesis is supported by several observed phenomena: hyperpnea-induced bronchial water losses are substantial; prolonged hyperpnea reduces the water replacement capability of the airways; hyperosmolar aerosol inhalation directly triggers bronchoconstriction; hyperosmolar responsive cells do exist within the airway; and increased duration of hyperpnea leads to steadily increasing osmolar changes.

Evidence against the water-loss hypothesis also exists, however. In particular, the hypothesis does not explain why the most major constriction of the airways occurs after cessation of hyperpnea. Nor does the hypothesis explain how vasoconstrictors can blunt EIA and hyperventilation-induced asthma (HIA) in controlled settings.

The postexertional airway-rewarming hypothesis states that the initial airway heat loss associated with hyperpnea causes a vascular dilation and edema that physically narrows the airway. This hypothesis is supported by several facts: some vasodilation in systemic vasculature occurs after cold exposure; alpha-adrenergic agonists limit HIA; vascular volume redistribution by antishock trousers limits HIA; and the time



required for redistribution of blood flow theoretically matches the vessel rewarming time. Evidence against this theory includes the fact that in animals, pulmonary blood flow increases during cold-air HIA and decreases during the posthyperpnea period, and no direct evidence exists to support the possibility that rewarming hyperemia occurs in lung vessels or airway tissue. Moreover, minimum airway temperature is reached within two minutes, showing that bronchoconstriction is delayed even though prolonged hyperpnea causes no further temperature change.

The cellular mechanism of this process has yet to be defined. Sensory neurons have been implicated in animal models as possible pathways but have not been identified in humans.

Clinical Manifestations of EIA

The pathophysiologic mechanisms of asthma result in a number of physiologic changes occurring within the pulmonary tree. These changes include bronchospasm (the main component of EIA), hypoxia, hypercarbia (if airway obstruction is sufficiently severe, ie, FEV₁ measured at ≤25% of predicted value), edema of the bronchial walls, mucosal sloughing, and excessive quantities of highly viscous mucus. The most major changes seen in patients with EIA are bronchospasm and edema. If a late-phase reaction occurs, all these factors may be involved.

Clinically, this set of changes results in EIA symptoms that include dyspnea, wheezing, coughing, chest tightness or pain, phlegm (occasionally), and abdominal pain (rarely). Onset of symptoms usually occurs as physical activity ceases or 5-10 minutes after resumption of activity. Symptoms resolve and pulmonary function tests return to normal about 20-30 minutes after onset of symptoms. The refractory period (in which further symptoms cannot be induced) can last from 30 minutes to two hours.

Conditions likely to elicit EIA include cold, dry ambient environment; high levels of air pollution and airborne allergens; and strenuous physical activity, whether of a type that tends to be highly asthmogenic (eg, long-distance running, bicycling, basketball, soccer, rugby, ice hockey, ice skating, cross-country skiing) or moderately asthmogenic (eg, gymnastics, karate, wrestling, boxing, sprinting, golf, football, baseball, downhill skiing, isometrics, diving, short-distance swimming). In addition, EIA may be elicited by individual factors such as poor control of underlying asthma, recent respiratory infection, and recent exposure to major airborne allergens.

Diagnosis of EIA

EIA is diagnosed primarily by medical history. In asthmatic persons, exercise should be assumed to exacerbate asthma. Atopic persons with or without asthma should be questioned carefully regarding possible EIA symptoms. Persons who complain of cough, wheezing, dyspnea, chest pain, or chest tightness after beginning aerobic activity should be questioned further regarding other symptoms related to EIA. Children who cannot keep pace with their peers during physical activity should be asked whether breathing is difficult during the activity. Any child or young adult who has stopped physical activity for reasons such as "I just couldn't do it anymore" should also be questioned further.

When the diagnosis of EIA is suspected in the patient who is not known to have asthma, a trial of prophylactic drug therapy may be initiated first. This approach to diagnosis is reasonable in persons who can give reliable feedback about their symptoms and about their response to medication. If any question exists about the accuracy of the patient's reporting, however, the diagnosis must be confirmed by EIA testing.

EIA testing is best done by a free-run challenge in which the patient is asked to run at full speed for 3-5 minutes, attaining a heart rate at least two thirds of their target heart rate (or 180 beats per minute in

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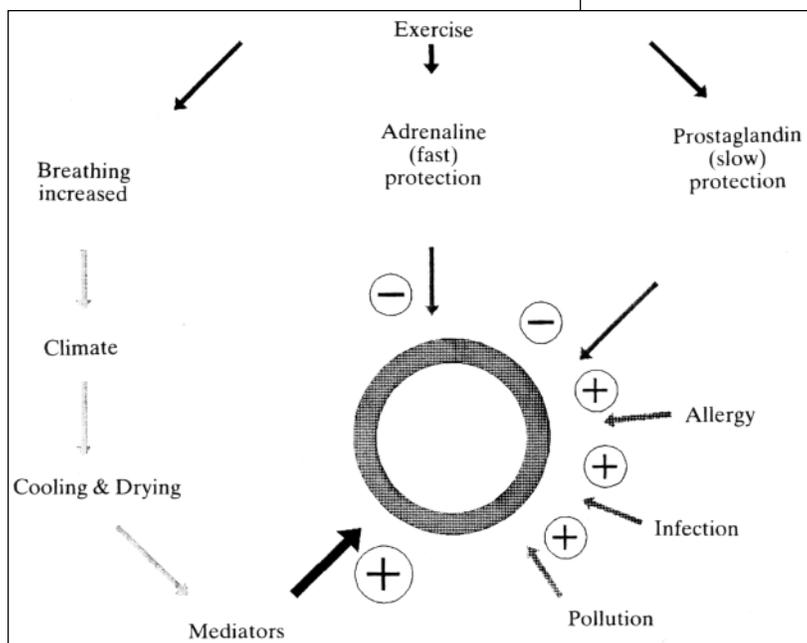


Figure 3. Model of pathways involved in exercise-induced asthma.

(Reproduced by permission of the author and publisher from: Godfrey S, Bar-Yishay E. Exercise-induced asthma revisited. *Respir Med* 1993;87:338.)

children). The patient should stop after five minutes (or earlier if symptoms arise). Pulmonary function should be measured (by FEV₁ or by PEFR) at baseline,

immediately after stopping the run, and at 5, 10, 15, 20, and 30 minutes after the activity is completed. A decrease of ≥15% in FEV₁ or PEFR is diagnostic of

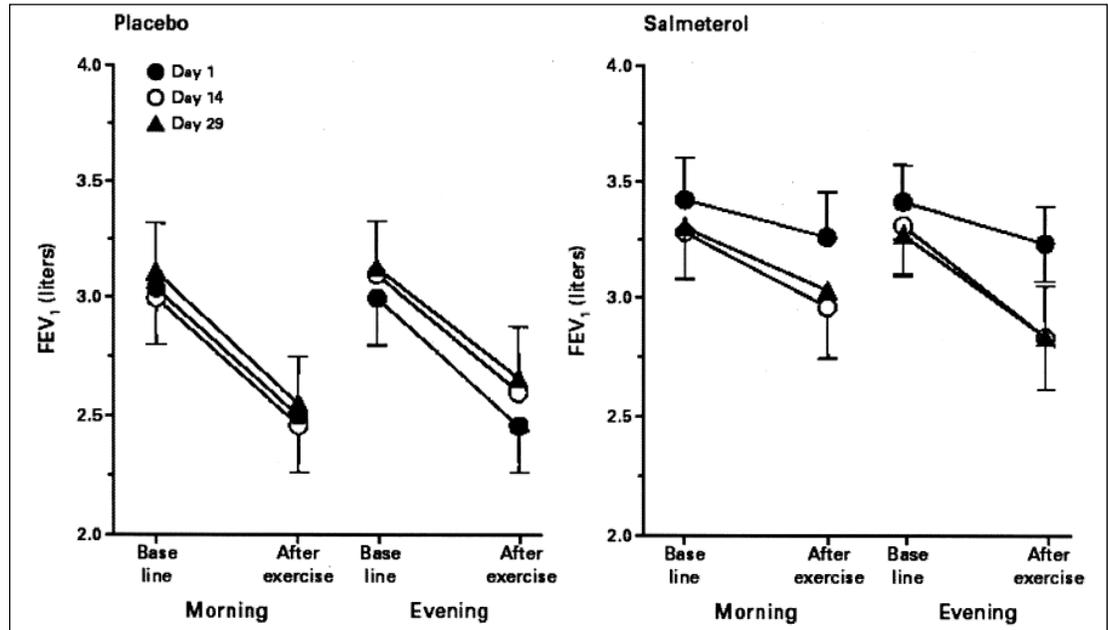


Figure 4. Plot shows absolute effects of placebo and salmeterol on response to exercise over time. Morning baseline data were recorded after administration of study drugs. Values are mean ± SE.

(Reproduced by permission of the publisher from: Nelson JA, Strauss L, Skowronski M, Ciufo R, Novak R, McFadden ER Jr. Effect of long-term salmeterol treatment on exercise-induced asthma. *N Engl J Med* 1998;339:144.¹⁰)

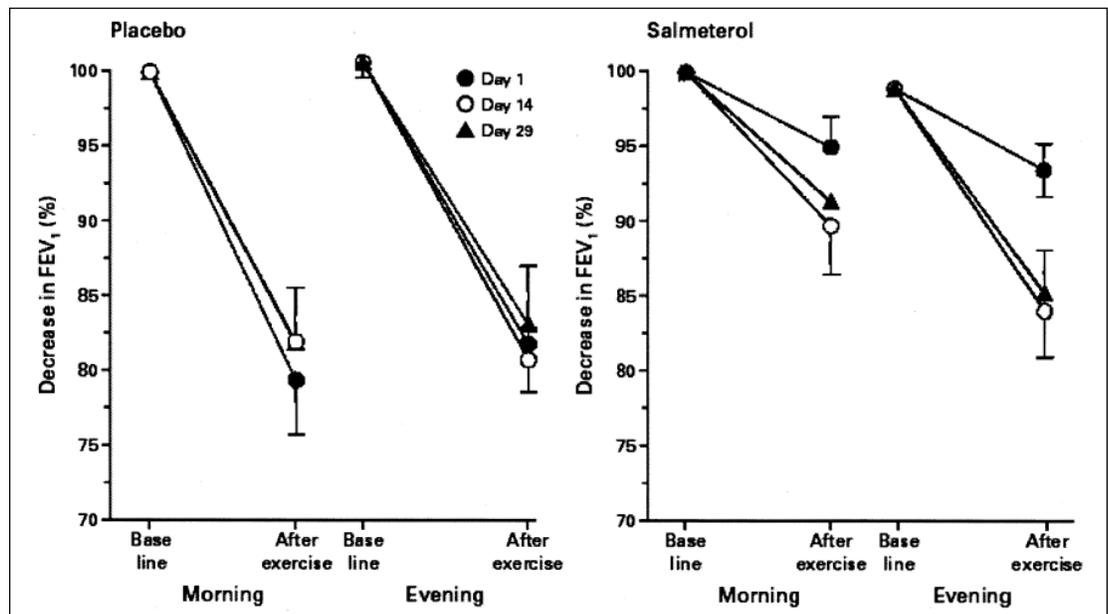


Figure 5. Plot shows relative effects of placebo and salmeterol on response to exercise over time. Morning baseline data were recorded after administration of study drugs. Values are mean ± SE.

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EIA, assuming that the breathing efforts are well done. Clinicians should be prepared to administer a bronchodilator during or after the test. Sensitivity of exercise testing ranges from 55% to 80%, and specificity is 93%.³ Testing should not be done during episodes of asthma.

Treatment of EIA

EIA can be treated by several methods. The purpose of treatment is to maximize the patient's ability to participate actively in aerobic activity, whether it be recreation, serious athletics, work-related activity, or school-related activity. Treatment is intended to enhance patients' sense of self-worth, socialization, physical conditioning, and even to help them retain employment. Can we successfully treat EIA? Yes! The 1988 US Olympic Team included 67 (of 597) members affected with EIA. These athletes won 15 gold, 21 silver, and 5 bronze medals in multiple sports, including long-distance running.

To successfully control symptoms of EIA in any person with known asthma, excellent control of the underlying asthma is necessary.

Nonpharmaceutical Treatment of EIA

Medication is not the only way to treat EIA: Type of physical activity done by the patient is also important. Clinicians should encourage patients to choose less asthmogenic activities whenever possible. Ambient conditions should be considered as well: The more humid and warmer the air, the less the chance of stimulating EIA. Thus, indoor activity is less likely to trigger EIA. Wearing a mask or face covering (ie, a scarf) may help to warm and humidify outdoor air. Physical activity on days of high air pollution should be avoided or minimized (early-morning activity may reduce exposure in some cities). For asthmatic persons who are highly sensitive to pollen, activity should be timed to occur when diurnal pollen counts are lowest.

The refractory period also may be used beneficially. Encouraging an athlete to exercise in several 2- to 3-minute increments as "warm-ups" 10-20 minutes before the main physical activity may induce a period of up to one hour during which EIA does not develop. This precaution benefits only those whose duration of planned activity is short (eg, a sprinter).

Pharmaceutical Treatment of EIA

Several factors must be considered when initiating treatment: Does the patient have predictable periods

of aerobic activity (eg, jogs each morning only, is a day laborer, or is a playful 4-year-old child)? Are the ambient conditions in which activity takes place controllable? Can the patient effectively use a metered-dose inhaler? How long will the physical activity continue? How intense aerobically is the physical activity?

In general, drug therapy is effective for patients whose physical activity is brief and predictable and who can use a metered-dose inhaler correctly. If physical activity continues for more than 2-3 hours or if the patient cannot use a metered-dose inhaler effectively, consideration of oral medication may be warranted.

Treatment is selected from three types of medication: beta-adrenergic drugs, mast cell inhibitors, and leukotriene antagonists.

Beta-adrenergic drugs are an excellent first-choice medication for treating patients whose activity must be limited in duration (ie, <3 hours). These drugs can be used 15 minutes before activity is begun and are relatively safe if they are not overused. Because bronchospasm is the main component of EIA, these drugs are highly effective. Albuterol and terbutaline are most commonly used. Recent data indicate that salmeterol can remain effective for 10-12 hours (Figure 4)¹⁰; duration of the effect diminishes with continued use (Fig 5).¹⁰ Clinicians should emphasize to patients that salmeterol dosing should never be repeated more frequently than every 12 hours because overuse can induce cardiac toxicity. Oral beta-adrenergic agents may also be used but must be taken at least 30-45 minutes before the activity is begun. Beta-adrenergic agents may cause more side effects when taken orally than when they are administered by metered-dose inhaler.

Another group of medications used to treat EIA are called mast cell inhibitors, but whether inhibition of mast cells is their primary mode of action is unclear. These medications are an excellent choice for preventing EIA, and they have an excellent safety profile. Cromolyn and nedocromil also have the advantage of blocking early-phase and late-phase responses. These drugs are delivered by metered-dose inhaler (2-3 sprays administered 10-15 minutes before onset of activity) and may be needed after every 2-4 hours of continuous activity.

Leukotriene antagonists constitute the third group of medications used to treat EIA. Of these drugs, montelukast (Singulair) has recently been shown effective in preventing EIA. Long-term use (ie, use longer than 12 weeks) was not associated with shortened duration of action or with dimi-

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nution in protection offered as measured by FEV₁.¹¹ The medication is given orally in a single dose (tablet) each day. Because long-term side effects of these medications are not yet known, the drugs should be used with caution. Montelukast is not approved for use in children younger than six years. Other medications (eg, inhaled steroids) have been used but are generally used to decrease airway hyperreactivity; to achieve this result, a month or more of moderate- to high-dose daily use may be required. These drugs are best reserved for use in controlling asthma that is not specifically related to exercise. Theophylline can be used and may be beneficial, but timing its use to the activity is more difficult, and its side-effect profile is not as favorable as for the other medications listed above.

Overall, medications benefit 60% to 80% of patients susceptible to EIA and reduce the decrease in FEV₁ in these patients from 40% to 80%.

Athletic Competition and EIA

Diagnosis and treatment of athletes participating in formal competition is essentially the same as for other persons except that competitive athletes tend to recognize even small changes in airway function, and this small amount of change may not respond noticeably to medication therapy. In addition, the degree of response achieved by using these medications may not warrant use of the large amounts of medication needed to relieve all symptoms. This consideration should be discussed carefully with each affected athlete.

In addition, athletes in competition are also likely to behave stoically when having physical discomfort and thus may underreport symptoms. Detailed questions about performance and the symptoms of EIA are therefore especially necessary for these persons.

Each sport's governing body has established its own rules requiring disclosure by athletes regarding their use of medications as well as the acceptability of specific medications for athletes participating in formal competition. Athletes participating in formal com-

petition should obtain these rules from their sport's governing body.

The US Olympic Committee Drug Hotline can be reached at 1-800-233-0393.

Conclusion

EIA is a common problem that affects millions of people annually in the United States. It is often unrecognized by patients and physicians; a reasonable index of suspicion and some simple screening questions lead to a presumptive diagnosis in most cases. EIA is treated pharmaceutically and using nonpharmaceutical approaches. Most important, control of any underlying asthma is essential for control of EIA. The importance of recognizing and treating EIA is essential if we are to provide all affected persons with the opportunity for better overall health, better socialization, and better self-image. ❖

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