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# Keeping Children With Exercise-induced Asthma Active

Henry Milgrom, MD, and Lynn M. Taussig, MD

**ABSTRACT.** Exercise-induced bronchospasm, exercise-induced bronchoconstriction, and exercise-induced asthma (EIA) are all terms used to describe the phenomenon of transient airflow obstruction associated with physical exertion. It is a prominent finding in children and young adults because of their greater participation in vigorous activities.[1] The symptoms—shortness of breath, cough, chest tightness, and wheezing—normally follow the brief period of bronchodilation present early in the course of exercise. Bronchospasm typically arises within 10 to 15 minutes of beginning exercise, peaks 8 to 15 minutes after the exertion is concluded, and resolves about 60 minutes later,[2] but it also may appear during sustained exertion.[3] EIA occurs in up to 90% of asthmatics and 40% of patients with allergic rhinitis; among athletes and in the general population its prevalence is between 6% and 13%.[4,5]

EIA frequently goes undiagnosed. Approximately 9% of individuals with EIA have no history of asthma or allergy.[1] Fifty percent of children with asthma who gave a negative history for EIA had a positive response to exercise challenge.[6] Among high school athletes, 12% of subjects not considered to be at risk by history or baseline spirometry tested positive.[5] Before the 1984 Olympic games, of 597 members of the US team, 67 (11%) were found to have EIA. Remarkably, only 26 had been previously identified, emphasizing the importance of screening for EIA even in well-conditioned individuals who appear to be in excellent health.[1,7]

The severity of bronchospasm in EIA is related to the level of ventilation, to heat and water loss from the respiratory tree, and also to the rate of airway rewarming and rehydration after the challenge.[8,9] Postexercise decrease in the peak expiratory flow rate of normal children may be as much as 15%; therefore, only a decrease in excess of 15% should be viewed as diagnostic. EIA is usually provoked by a workload sufficient to produce 80% of maximum oxygen consumption; however, in severe asthmatics even minimal exertion may be enough to produce symptoms.[1] Patients with normal lung function at rest may have severe air flow limitation induced by exercise,[10] and as many as 50% of patients who are well-controlled with inhaled corticosteroids still exhibit EIA.[11] A challenge of sufficient magnitude will provoke EIA in all patients with asthma.[12]

*Pharmacologic Therapy.* Exercise, unlike exposure to allergens, does not produce a long-term increase in airway reactivity. Accordingly, patients whose symptoms manifest only after strenuous activity may be treated prophylactically and do not require continuous therapy.[13] Most asthma medications, even some unconventional ones such as heparin, furosemide, calcium channel blockers, and terfenadine, given before exercise, suppress EIA.[14,15] McFadden accounts for the efficacy of these disparate classes of drugs by their potential effect on the bronchial vasculature that modulates the cooling and/or rewarming phases of the reaction.[16] Short-acting $\beta$-agonists provide protection in 80% to 95% of affected individuals with insignificant side effects and have been regarded for many years as first-line therapy.[17] Two long-acting bronchodilators, salmeterol and formoterol, have been found effective in the prevention of EIA.[18–21] A single 50-$\mu$g dose of salmeterol protects against EIA for 9 hours; its duration appears to wane in the course of daily therapy.[22–24] Cromolyn sodium is highly effective in 70% to 87% of those diagnosed with EIA and has minimal side effects.[17] Nedocromil sodium provides protection equal to that of cromolyn in children.[25]

Children commonly engage in unplanned physical activity and sometimes are not allowed to carry their own medication. Thus, a simple long-acting regimen given at home is likely to be more effective than short-acting drugs that must be administered in a timely manner. Although the 12-hour protection by salmeterol reported by Bronsky et al[18] may not persist with continued use, the 9-hour duration of action is a dependable finding,[22–24] and should be sufficient in most cases.

*Nonpharmacologic Approaches.* At rest, inspired air is warmed and humidified primarily in the nose and trachea. As the rate of ventilation increases, the air is conditioned predominantly in the intrathoracic airways. Breathing through the nose rather than the mouth or through a mask that reduces the loss of heat and moisture during physical exertion has been shown to minimize EIA.[26,27] A gradual cooling off, rather than sudden cessation of activity reduces the rate of rewarming of airways and protects against bronchospasm.[16] About 40% to 50% of patients with EIA experience a refractory period after an earlier exercise stimulus. This protection has a half-life of about 45 minutes and dissipates over 2 to 3 hours.[28] For this reason, a prolonged warm-up that includes brief periods of intense activity is beneficial for many subjects with EIA.[29]

In individuals with EIA, aerobic conditioning lessens the prospect of an asthma attack by reducing the ventilatory requirement for any activity. Although improved fitness of children with asthma is highly desirable, we must emphatically discourage patients from adopting the view that they can overcome their disease solely by being in good physical shape.

*Conclusions.* EIA is a common clinical problem that is not limited to patients with asthma. It is as frequent in athletes as in the general population. With appropriate therapy, 90% of individuals with EIA can control their symptoms and should be able to participate in any vigorous activity.[29] Those patients who are refractory may

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**not be taking their medication or may suffer from another condition, most likely vocal cord dysfunction.[30,31]**

**Exercise is a powerful trigger for asthma symptoms. For this reason, young patients may avoid vigorous activity with damaging consequences to their physical and social well-being. Parents may be reluctant to allow their youngsters with asthma to participate in athletics, and teachers may fear taking responsibility for a child's severe attack. All patients suspected of having asthma should be questioned about how much exercise they perform, their exercise tolerance, and symptoms after exertion. Those with a concerning history should have an exercise challenge. Early diagnosis coupled with practical, long-acting treatment regimes such as the one reported by Bronsky et al[18] should help these young people enjoy the benefits of an active lifestyle and fulfill their athletic potential.** ***Pediatrics*** **1999;104(3). URL: http://www.pediatrics.org/cgi/content/full/104/3/e38;** ***exercise-induced asthma, exercise-induced bronchospasm, exercise-induced bronchoconstriction.***

ABBREVIATIONS. EIA, exercise-induced asthma; $FEV_1$, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate.

Exercise-induced bronchospasm, exercise-induced bronchoconstriction, and exercise-induced asthma (EIA) are all terms used to describe the phenomenon of transient airflow obstruction associated with physical exertion. EIA is a problem for all age groups, but its effects are most prominent in children and young adults because of their greater participation in vigorous activities.[1] In this issue of *Pediatrics*, Bronsky and colleagues[18] report the results of a study of the suppression of EIA by salmeterol. Their randomized, double-blind, placebo-controlled, 3-way crossover protocol was conducted in 24 children with EIA.[18] The 3 treatment arms were placebo and salmeterol 50 $\mu$g delivered by 1 of 2 dry powder delivery devices, the Diskhaler (Glaxo Wellcome, Inc, Research Triangle Park, NC) or the Diskus (Glaxo Wellcome, Inc, Research Triangle Park, NC). Forced expiratory volume in 1 second ($FEV_1$) was measured before and after treadmill exercise challenges performed at 1, 6, and 12 hours after a single dose of drug or placebo. A decrease in $FEV_1$ was minimized or prevented by salmeterol powder delivered by either system for up to 12 hours; the decline in $FEV_1$ was unaffected by placebo.

## SYMPTOMS, INCIDENCE, AND PATHOPHYSIOLOGY OF EIA

The symptoms of EIA—shortness of breath, cough, chest tightness, and wheezing—typically follow a brief period of bronchodilation that is present early in the course of exercise. Bronchospasm may arise within 10 to 15 minutes of beginning exercise; it peaks 8 to 15 minutes after the exertion is concluded and resolves about 60 minutes later.[2] The existence of a much weaker delayed response 4 to 12 hours after exercise is the subject of controversy.[28,32] Although EIA characteristically develops after cessation of the physical activity, it may also appear during sustained exertion.[3]

EIA occurs in up to 90% of asthmatics and 40% of patients with allergic rhinitis; its prevalence in general population is between 6% and 13%; among athletes estimates reach 12%.[4,5] It is very likely that EIA frequently goes undiagnosed. Approximately 9% of individuals with EIA have no history of asthma or allergy.[1] Fifty percent of children with asthma who gave a negative history for EIA had a positive response to exercise challenge.[6] When high school athletes were screened for EIA, 12% of subjects not considered to be at risk by history or baseline spirometry tested positive.[5] Before the 1984 Olympic games, of 597 members of the US team 67 (11%) were found to have EIA. Remarkably, only 26 of these competitors who trained under close medical supervision had been previously identified, emphasizing the importance of screening for EIA even in well-conditioned individuals who appear to be in excellent health.[1,7] If EIA is underdiagnosed in the elite athlete then the problem must be even greater for the typical child.

Although EIA can be diagnosed clinically, it is best to confirm the observation in the laboratory by a decrease in the peak expiratory flow rate (PEFR) or $FEV_1$ $\geq$15% after exercise or hyperventilation. The occurrence of EIA generally requires a workload sufficient to produce 80% of maximum oxygen consumption; however, in severe asthmatics even minimal exertion may be enough to produce symptoms.[1] Patients with normal lung function at rest may have severe air flow limitation induced by exercise,[10] and as many as 50% of patients who are well-controlled with inhaled corticosteroids still exhibit EIA.[11] A challenge of sufficient magnitude will provoke EIA in all patients with asthma.[12] Postexercise decrease in the PEFR of normal children may be as much as 15%, and only a decrease in excess of 15% should be viewed as diagnostic.[1,6] Protocols based on duration of work or the achievement of specific heart rate may not incorporate all the relevant variables[33]; however, a challenge that consists of 6 minutes of continuous exercise at intensity sufficient to raise the heart rate to 80% of the maximum predicted usually yields satisfactory data. Variability in the reported incidence may result from inconsistent use of criteria for diagnosis, but it is important to note that a child's response to exercise may change markedly from day to day. It depends on the nature of the exercise, the ambient conditions, and the child's airway responsiveness that may be affected by viral infections, exposure to allergens, and the use of medications.

The evolution of understanding of EIA is captivating. Aretaeus, the Cappadocian, in the 2nd century AD documented that exercise is a trigger for asthma.[34,35] Aretaeus observed that

> . . . if from running, gymnastic exercises, or any other work, the breathing becomes difficult, it is called *Asthma* . . . The symptoms of its approach are heaviness of the chest; sluggishness to one's accustomed work, and to every other exertion; difficulty of breathing in running or on steep road; they are hoarse and troubled with cough . . . But, during the remissions, although they may walk about erect, they bear the traces of the affection.

Sir John Floyer, an English physician and an asthma patient himself, recognized near the end of the 17th

century that different types of exercise caused symptoms of varying intensity.[34,36] This work was confirmed and amplified by Godfrey,[15] who in 1975, demonstrated that free-range running was the strongest trigger for EIA causing an average 47% decrease in PEFR. Running on a treadmill was weaker causing a 33% decrease, and cycling 25%. Other forms of exercise such as swimming, kayaking, and walking, even if as strenuous as free range running, brought about only a 13% to 15% decrease in lung function.[34,37] This work identified the best forms of exercise to choose for asthma patients and also the best types for use in provocation challenges when the goal is the reliable induction of bronchospasm.

The severity of bronchospasm in EIA is related to the level of ventilation and to heat and water loss from the respiratory tree. The pathogenesis is attributable to the fluxes in heat and water that occur in the airways during conditioning of large volumes of air. Hyperventilation with 5.6% carbon dioxide results in marked bronchoconstriction even in the absence of exercise.[34] Reduction of the temperature and water content of inspired air enhances bronchoconstriction caused by isocapneic hyperventilation.[38] The rate and amount of water loss have been proposed as the main determinants of the extent of airway response,[39] but a prevailing current view, proposed by McFadden,[8,9] holds that the severity of EIA depends not only on airway cooling and drying, but also on the rate of airway rewarming and rehydration after the challenge. To give emphasis to this association McFadden and colleagues have proposed the term, "thermally induced asthma."

## MEDIATORS OF EIA

Mast cells, eosinophils. and alveolar macrophages, all resident in the airways, have the capacity to synthesize leukotrienes. Human mast cells readily degranulate in response to a change in osmolarity, constituting a link between the loss of water from hyperventilation during exercise and subsequent mediator release.[40] Concentrations of leukotrienes in the nasal lavage have been shown to rise fourfold after cold, dry air exposure in subjects with rhinitis.[41] Isocapneic hyperpnea is associated with increased concentrations of leukotrienes B4, C4, D4, and E4 in the bronchoalveolar lavage fluid,[42] and of leukotriene E4 in the urine of children with EIA after exercise challenge.[43]

The oral drug, zafirlukast, a D4 leukotriene receptor blocker, attenuates exercise-induced bronchoconstriction in children for 4 hours after dosing.[44] Both zafirlukast and another oral anti-leukotriene agent, zileuton, a 5-lipoxygenase inhibitor, suppress EIA by about 50%.[40] The inability of these agents to inhibit more than half of the EIA suggests that other mediators are also involved in this process. A single dose of the antihistamine, terfenadine 180 mg, inhibits EIA by approximately 35%.[45] It increases the intensity of the exercise required to provoke bronchospasm to the same extent as cromolyn. When the dose is raised beyond 180 mg, protection against the challenge does not increase. This suggests that histamine confers 35% of the immediate airway response to exercise challenge.

Thus, there is both direct and indirect evidence for a role of the leukotrienes and indirect evidence for the involvement of histamine in the generation of EIA. The mast cells are a source of both products. These cells are capable of inducing immediate bronchospasm after allergen exposure, but their degranulation has also been demonstrated after stimuli not mediated by immunoglobulin E such as cold dry air.[41,46] The effectiveness of such pharmacologic agents as cromolyn and nedocromil in EIA lends further support to a role for the mast cell.

Studies that have sought inflammatory mediators other than the leukotrienes in the peripheral blood and in the bronchoalveolar fluid during or after EIA have been largely unsuccessful. However, localized action of cells other than the mast cell cannot be excluded because of difficulties inherent in measuring mediators in secretions and in identifying the optimal time for obtaining samples.[46]

## PHARMACOLOGIC THERAPY

Exercise, unlike exposure to allergens, does not produce a long-term increase in airway reactivity. Accordingly, patients whose symptoms manifest only after strenuous activity may be treated prophylactically and do not require continuous therapy.[13] Most asthma medications, even some unconventional ones such as heparin, furosemide, calcium channel blockers, and terfenadine, given before exercise, suppress EIA.[14,15] McFadden[16] accounts for the efficacy of these disparate classes of drugs by their potential effect on the bronchial vasculature that modulates the cooling and/or rewarming phases of the reaction. Short-acting $\beta$-agonists provide protection in 80% to 95% of affected individuals with insignificant side effects and have been regarded for many years as first-line therapy.[17] Cromolyn sodium is also highly effective in 70% to 87% of those diagnosed with EIA and has minimal side effects.[17] Nedocromil sodium provides protection equal to that of cromolyn in children.[25] The preferred mode of administration for all these drugs is through metered dose inhalers using chlorofluorocarbons as a propellant.

The newest $\beta$-agonist to be introduced in the United States is salmeterol,[47,48] and another one, formoterol (not to be confused with the short-acting agent fenoterol), is under investigation. Both are long-acting bronchodilators, and both have been found effective in the prevention of EIA.[19–21] Salmeterol is not associated with rebound airway hyperresponsiveness, the masking of symptoms, or adverse effects.[49] A single 50 $\mu$g dose of salmeterol has been found to protect against EIA for 9 hours; its duration appears to wane in the course of daily therapy.[22–24]

More recently, alternative drug delivery systems have been introduced in part to reduce the emission of chlorofluorocarbons but also to devise methods of administration that may eliminate the need for coordination between inspiration and the actuation of the metered dose inhaler. Further, dry powder inhalers may provide more controlled delivery of a drug with

a greater proportion reaching the small airways.[50] The Diskhaler, a breath-activated, refillable inhalation device used with a sealed 4-blister dosage pack, is a dry powder delivery system that accomplishes the stated goals. Clinical trials have demonstrated that the Diskhaler is effective in the delivery of asthma medications. Its main disadvantage is the requirement for frequent reloading with new blister packs, an inconvenience that may undermine patient adherence. The Diskus is a multidose powder inhaler that delivers 60 premeasured, sealed doses of drug, providing medication for up to 1 month rather than only 1 or 2 days. It is relatively easy to use, and it provides a counter that displays the number of doses remaining in the device. At the range of inspiratory flow rates encountered in asthma patients (30–90 L/min), the dose delivered via the Diskus remains at approximately 90% of the label claim. The two systems have been shown previously to be comparable in the delivery of salmeterol.[51]

## BENEFITS OF LONG-ACTING DRUGS

Inhaled short-acting β-agonists are effective as bronchodilators for up to 4 hours, but their usefulness as prophylactic agents for EIA is under 2.5 hours.[52] Children commonly engage in unplanned physical activity and when exercise is scheduled, it frequently takes place on school grounds where they may not allowed to carry their own medication. Older children may be unwilling to take medicine in the presence of their schoolmates. Thus, a simple long-acting regimen given at home is likely to be more effective than short-acting drugs that must administered in a timely manner. Although the 12-hour protection by salmeterol reported by Bronsky et al may not persist with continued use, the 9-hour duration of action is a dependable finding, and should be sufficient in most cases.[22–24]

The Expert Panel, convened by the National Heart Lung and Blood Institute, has issued guidelines for the treatment of asthma that include recommendations for EIA. These guidelines embrace a stepwise approach to treat patients with disease of varying severity. The Panel endorsed the use of short-acting β-agonists and salmeterol, nedocromil, and cromolyn for the prevention of EIA.[53] Experience with salmeterol is limited, but it clearly appears promising. Additional approaches that may offer more sustained control of EIA include other long-acting β-agonists and, as suggested above, a combination of an antileukotriene agent with a long-acting antihistamine (H. S. Nelson, personal communication, April 7, 1999).

## NONPHARMACOLOGIC THERAPY

At rest, inspired air is warmed and humidified primarily in the nose and trachea. As the rate of ventilation increases, the air is conditioned predominantly in the intrathoracic airways. Breathing through the nose rather than the mouth or through a mask that reduces the loss of heat and moisture during physical exertion has been shown to minimize EIA.[26,27] About 40% to 50% of patients with EIA experience a refractory period after an earlier exercise stimulus. This protection has a half-life of about 45 minutes and dissipates over 2 to 3 hours.[28] For this reason, a prolonged warm-up that includes brief periods of intense activity is beneficial for subjects with EIA.[29] A gradual cooling off, rather than sudden cessation of activity reduces the rate of rewarming of airways and similarly protects against bronchospasm.[16]

Physical fitness raises exercise tolerance and capacity resulting in an increase in oxygen uptake, a reduction in ventilatory requirement, cardiac frequency, and lactic acid production at any given workload in all individuals.[54] Although there is no consistent evidence that physical training decreases the incidence of EIA or improves pulmonary function, it allows patients to increase their exercise load before reaching the threshold for EIA.[54,55] In individuals with EIA, aerobic conditioning lessens the prospect of an asthma attack by reducing the ventilatory requirement for any activity. Although improved fitness of children with asthma is highly desirable, we must emphatically discourage patients from adopting the view that they can overcome their disease solely by being in good physical shape.

## CONCLUSIONS

EIA is a common clinical problem that is not limited to patients with asthma. It affects at least 11% of athletes, many of whom compete successfully in aerobic events. The 1984 US Summer Olympic team included 67 athletes with EIA who won 41 medals, 15 of them gold.[29] With appropriate therapy, 90% of patients with EIA can control their symptoms and should be able to participate in any vigorous activity.[29] Those patients who are refractory may not be taking their medication or may suffer from another condition, most likely vocal cord dysfunction.[30,31]

Exercise is a powerful trigger for asthma symptoms. For this reason, young patients may avoid vigorous activity with damaging consequences to their physical and social well-being. Parents may be reluctant to allow their youngsters with asthma to participate in athletics, and teachers may fear taking responsibility for a child's severe attack. All patients suspected of having asthma should be questioned about how much exercise they perform, their exercise tolerance, and symptoms after exertion. The same inquiry should be addressed to children with chronic cough, allergic rhinitis, and even those at risk for developing asthma such as first degree relatives of asthma patients and children with atopic dermatitis. Those with a persuasive history should have an exercise challenge. Early diagnosis coupled with practical, long-acting treatment regimes, such as the one reported by Bronsky et al,[18] should help these young people enjoy the benefits of an active lifestyle and fulfill their athletic potential.

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