REVIEW ARTICLE

Management of Exercise-Induced Bronchospasm in Children

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Bronchospasm precipitated by exercise is often indistinguishable from bronchospasm produced by other stimuli. Symptoms result from airflow limitation and include wheezing, cough, chest tightness, dyspnea and sometimes hypoxemia. The prevalence of exercise-induced bronchospasm varies from 30%-90%, but virtually all patients with current asthma will experience a decrease in lung function if the exercise is sufficiently vigorous, especially in cold, dry environmental conditions. Exercise-induced bronchospasm is more prevalent in children than in adults, probably because children are physically more active. It is also more prevalent among elite winter sports athletes. The pathogenesis of exercise-induced bronchospasm involves a defect in respiratory heat exchange that probably triggers mast cell and eosinophil release of bronchoconstricting mediators. The goal of therapy is prevention of symptoms. This may be accomplished by pre-treating patients with isolated exercise-induced bronchospasm using an inhaled rapid-onset β2-adrenergic agonist before a scheduled activity or by treating the underlying inflammation when exercise-induced bronchospasm is part of the clinical syndrome of persistent asthma. In the later instance, either an inhaled corticosteroid, an oral leukotriene modifier, or a combination of both, depending on severity, may be required to prevent exercise-induced bronchospasm associated with activities of daily living. In addition, some of these patients may still require pre-treatment with a short-acting inhaled β2-agonist before a scheduled vigorous activity, especially in very cold ambient temperatures. Because the duration of bronchoprotection decreases with daily use (tachyphylaxis), long acting β2-adrenergic agonists (e.g., formoterol, salmeterol) have a limited role in treating exercise-induced bronchospasm.

Keywords: exercise-induced bronchospasm, pediatrics

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INTRODUCTION

Exercise-induced bronchospasm, exercise-induced asthma, and thermally-induced asthma are synonymous terms describing acute airway narrowing that develops immediately *after* vigorous physical activity in patients with asthma. Although estimates of the prevalence of this condition have varied from 30–90%,[1] virtually all patients with current asthma will experience a decrease in lung function if the exercise is intense enough,[2] especially in very cold, dry environmental conditions. It may be more prevalent in children than in adults, probably because children are physically more active. Also, the prevalence is higher in elite winter sport athletes than in summer Olympic participants.[3] Exercise-induced bronchospasm may be just one of the many triggers in persistent asthma or may be the primary clinical manifestation in patients with mild intermittent disease (i.e., "isolated exercise-induced bronchospasm"). Often patients with isolated exercise-induced bronchospasm also report asthma symptoms in association with viral upper respiratory tract infections, but are free of symptoms for extended periods in the absence of these triggers.

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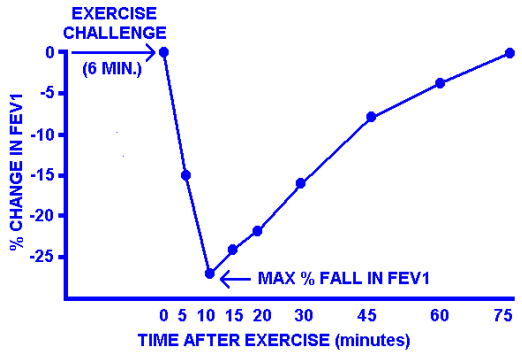
PATHOPHYSIOLOGY

Strenuous exercise is a potent, naturally occurring provocation of airway narrowing in patients with asthma, but does not elicit broncho-

Figure 1. Schematic representation of the change in forced expiratory volume in the first second (FEV1) typically seen immediately, and for the first 75 min after exercise in an individual with exercise-induced bronchospasm. FEV1 reaches a nadir within 5-10 min after exercise and spontaneously recovers to within 5% of the pre-exercise value by about 60 min. Adapted from Leff et al.[4]

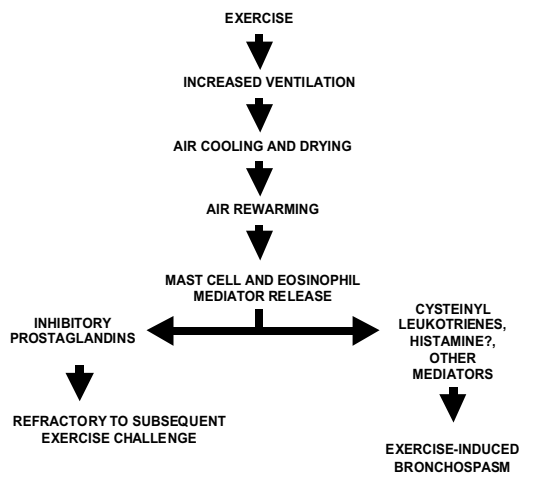


spasm in those who do not have the disease. The typical pattern of response during exercise is initial bronchodilation that disappears when exercise stops. Airway narrowing begins almost immediately thereafter. The decrease in lung function reaches a peak in 5–10 minutes and then spontaneously remits completely within 75 minutes (Figure 1).[4] A positive exercise-induced bronchospasm response is defined as a ≥15% reduction in the forced expired volume in the first second (FEV1) of a forced vital capacity maneuver.[5]

The pathogenesis of exercise-induced bronchospasm continues to be debated among pulmonary physiologists. Despite the controversy, the general pathology behind exercise-induced bronchospasm involves a defect in respiratory heat exchange that probably triggers mast cell and eosinophil release of bronchoconstricting mediators (Figure 2).[6] The severity of airway narrowing that occurs following exercise is a function of the absolute quantity of air exchanged per minute (minute ventilation), the temperature of inhaled air, and the water content of the inspired gas.[7] For a given set of inspired air conditions, a higher minute ventilation results in greater airway narrowing. Thus, strenuous exertion such as running or pedaling a bicycle uphill, evokes a greater response than does walking or pedaling a bicycle over level ground. For a given level of minute ventilation, cooling and drying the inspired air exacerbates the exercise-induced bronchospasm. Importantly, inhaling air that is conditioned to match body temperature and humidity totally prevents exercise-induced bronchospasm.[8] It is now generally accepted that the pathogenesis of exercise-induced airway obstruction is closely associated with the conditioning of inspired air.[9] The purpose of this conditioning process is to heat and humidify the inspired air so that by the time it reaches the alveoli, it is fully saturated with water vapor at body temperature. The net effect of these thermal exchanges on inspiration is to cool the airway mucosa. Then, as warm humidified air is exhaled, recovery of both heat and water occurs, from the air to the mucosa. As the airways are not perfect heat exchangers, only about one third of the heat transferred to the air during inspiration is reclaimed during expiration. However, experimental evidence indicates that airway cooling alone is only one variable and must be followed by rapid airway rewarming for bronchoconstriction to occur.[9] In fact, exercise-induced bronchospasm is more intense when subjects breathe warm humidified air immediately after exercise.[10]

Many investigators argue that mediators released from mast cells and eosinophils in the airways play an important role in the pathogenesis of exercise-induced bronchospasm.[6] However, the results of experiments designed to document this association have been inconsistent, and the issue remains controversial. Studies searching for various inflammatory mediators in blood,

Figure 2. Schematic representation of the proposed pathogenesis of exercise-induced bronchospasm. Development of exercise-induced bronchospasm involves a defect in respiratory heat exchange that probably triggers mast cell and eosinophil release of bronchoconstricting mediators.



urine and bronchoalveolar lavage fluid before and after exercise have produced conflicting results.[11,12] Drugs with activity against inflammatory cells (e.g., inhaled corticosteroids)[13,14] or their secretory products (e.g., leukotriene modifiers)[4,15] are often effective in attenuating exercise-induced bronchospasm. Since urinary excretion of leukotriene E_4 is increased during exercise-induced bronchospasm [16] and leukotriene biosynthesis inhibitors[17] and receptor antagonists attenuate exercise-induced bronchospasm,[4,15,16,18-20] it is likely that release of these mediators of inflammation plays an important but not exclusive role in the pathogenesis of exercise-induced bronchospasm. In contrast, cetirazine,[21] a potent H1-receptor antagonist, and high doses of loratidine[22] do not attenuate exercise-induced bronchospasm even though human lung mast cells release histamine *in vitro.* These data suggest that histamine is not released in sufficient quantities *in vivo* to play an important role in exercise-induced bronchospasm. Lastly, McFadden[23] has hypothesized that rapid expansion of blood volume in peribronchial vasculature plexi may be an important cause of airway narrowing during exercise-induced bronchospasm, but so far this hypothesis has not been tested.

CLINICAL FEATURES

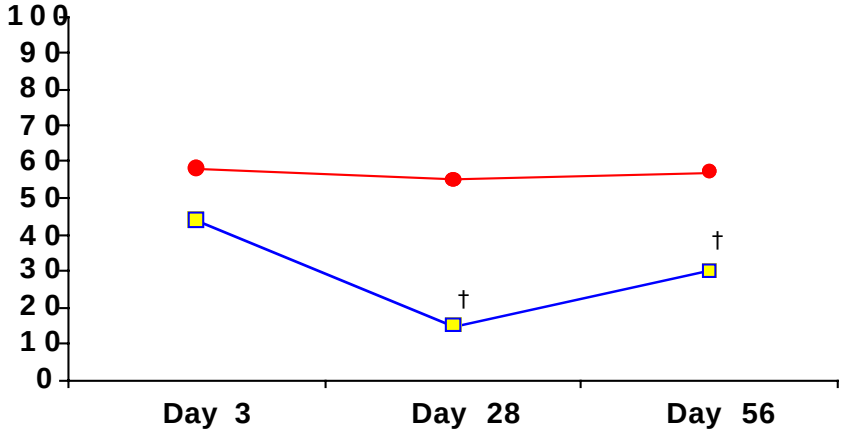
Asthma attacks precipitated by vigorous exercise are indistinguishable from symptoms produced by other stimuli. They include wheezing, cough, chest tightness and dyspnea in association with airflow limitation and sometimes hypoxemia. For symptoms to occur, exertion needs to be both vigorous and sustained. During exercise the airways actually dilate and only after the

TABLE. Medications documented to attenuate exercise-induced bronchospasm

Drug	Dosage Form	Dose	Relative Efficacy *				Reference
			Single Dose		Multiple Doses		
			Intensity †	Duration	Intensity †	Duration	
β2-adrenergic agonist							
Albuterol	MDI, DPI	200–400 μg	++++	1-2 h	paradoxical worsening	0	29, 40, 41
Formoterol	DPI	9–12 μg	++++	8 h	unknown	unknown	42
Salmeterol	MDI, DPI	42–50 μg	++++	9 h	++++	<4	18, 19, 33–36
Corticosteroids							
Budesonide	MDI	400 μg/d	Not effective	0	++++	≥12	13
Fluticasone	MDI	200 μg/d	Not effective	0	++++	≥12	14
Mast-Cell Stabilizers							
Cromolyn	Nebulizer	20 mg	+++	2 h	+++	2	43
	MDI	2 mg	++	2 h	++	2	43, 44
Leukotriene Modifiers							
Montelukast	PO	5 mg	++	20 h	++	20 h	4, 18–20
Zafirlukast	PO-fasting	10 mg	++	12 h	++	12 h	15
Theophylline							
Rapid Release	PO	At serum concentration >10 μg/mL	+++	<6 h	+++	<6h	45, 46

*= There are few comparative studies and none comparing all classes of drugs. These are the author's estimates of relative efficacy based on an aggregate of published reports; †= Attenuation compared to placebo (% protection); ++++ = ≥90%; ++ =50%

Figure 3. Mean percent protection from exercise-induced bronchospasm in 197 subjects (age 14–45 yr). Subjects were randomized to receive montelukast 10 mg once daily (•) or inhaled salmeterol 50 μg twice daily (□) in a double blind, double-dummy, parallel group designed study. Standardized exercise challenges were performed at the trough of each regimen in the late afternoon 9 h after salmeterol and 21 h after the last dose of montelukast. Percent protection was calculated from the area under the post-exercise FEV1-time curve. Treatment with montelukast and salmeterol were equivalent at day 3. At weeks 4 and 8, however, salmeterol treated subjects had significantly less bronchoprotection against exercise (i.e., tachyphylaxis) compared to treatment with montelukast. Adapted from Villaran et al.[19] The † symbol indicates P<0.002.



work is stopped, do airflow limitation and symptoms develop. The inability to complete a given activity because of tachypnea and dyspnea is usually caused by a lack of fitness or pre-existing airflow limitation and not exercise-induced bronchospasm. This time course of symptom appearance is important in the diagnosis of exercise-induced bronchospasm. For example, shortness of breath that develops during exercise but improves afterwards, should raise the specter of an alternative diagnosis. Subsequent to a single exercise period, there is a refractory period of about an hour or less during which the same level of activity does not produce exercise-induced bronchospasm. This may result from mast cell release of prostaglandins (e.g., PGE_2) that inhibit exercise-induced bronchospasm.[24]

The intensity of airway responsiveness to exercise is affected by the underlying state of airway reactivity, and the temperature and humidity of ambient air. However, it can't be predicted by the baseline FEV1.[25] The intensity of bronchospasm required to produce symptoms varies between patients, as well as within the same patient. Airway inflammation and exposure to allergens[26] or viral respiratory infections[27] increase airway responsiveness to exercise. For example, in a patient with persistent asthma, the magnitude of the post-exercise decrease in FEV1 strongly correlates with the provocative concentration of histamine required to produce a 20% decrease in FEV1 (PC_{20}).[28] Consequently, a standardized exercise challenge can be used in place of histamine or a methacholine challenge as a diagnostic test for asthma, to measure airway responsiveness and the long-term effects of medications such as inhaled corticosteroids.[5]

DIAGNOSIS

The initial diagnosis of exercise-induced bronchospasm is based upon clinical history and is confirmed by response to therapy. A 200–400 μg dose of albuterol (i.e., 2–4 actuations), delivered by metered-dose inhaler or dry powder inhaler 15 minutes before an activity, should completely prevent symptoms.[29] If this does not occur, the clinician should refer the patient to an asthma specialist who can perform a standardized exercise challenge test and consider alternative diagnoses such as vocal cord dysfunction or exercise-induced hyperventilation,[30] which can masquerade as exercise-induced bronchospasm. A ≥15 % decrease in FEV1 after a standardized 6-minute period of exercise at >80% of maximum aerobic capacity confirms the diagnosis of exercise-induced bronchospasm.[5] In patients with a high level of fitness or elite athletes, a higher level of workload, a longer duration of exercise or breathing cold dry air during the chal-

lenge, may be required to induce bronchospasm.[3]

MANAGEMENT

The management of exercise-induced bronchospasm in children depends upon the clinical pattern of asthma in the individual patient and the activities that induce symptoms. The principle aim is to prevent exercise-induced bronchospasm so that the patient can participate in whatever activities they choose, including competitive sports. Both warm-ups before and cool-downs (e.g., a slow decrease in activity rather than abrupt cessation) after a scheduled activity that induces symptoms should be recommended.[31] Since this may not be sufficient and isn't practical for increases in activity that are part of daily living, such as running up stairs to get to class on time, pharmacologic prophylaxis is generally required (Table). Some clinicians encourage their patients to exercise indoors when temperatures outside are near freezing or lower unless they are participating in team sports. Such a recommendation would prevent a child from enjoying ice skating or cross-country skiing. Although we have no experience with this in Florida, it seems to us that pharmacologic therapy should be tried before recommending such a limitation.

EXERCISE-INDUCED BRONCHOSPASM ASSOCIATED WITH PERSISTENT ASTHMA

When exercise-induced bronchospasm is part of persistent asthma, therapy must first be directed toward reducing the underlying airway inflammation with daily maintenance medication. In mild persistent asthma, an inhaled corticosteroid or a leukotriene receptor antagonist such as montelukast[4,20] (Singulair, Merck & Co., Whitehouse Station, NJ) or zafirlukast[15] taken fasting (Accolate, AstraZeneca, Wilmington, DE) may be sufficient. In patients with very mild disease, there is no evidence that inhaled corticosteroids offer an advantage over leukotriene modifiers which are more convenient and patients take more consistently.[32] We prefer montelukast because food does not affect absorption, it is dosed once a day, it does not elevate liver enzymes and has no clinically important drug-drug interactions. However, in children with moderate persistent asthma, one of the more potent inhaled corticosteroids such as budesonide[13] (Pulmicort, AstraZeneca, Wilmington, DE) or fluticasone[14] (Flovent, GlaxoSmithKline, Research Triangle Park, NC), delivered by an age-appropriate method, is usually required. Older, less potent, inhaled corticosteroids (e.g. triamcinolone, flunisolide) might be effective, but their effects on exercise-induced bronchospasm have not been studied. In addition, they are less convenient because they require more actuations per day than the newer, more potent agents.

It is common for short-acting β2-adrenergic agonists to be prescribed before exercise in all children regardless of their asthma phenotype. However, regular twice-daily use of inhaled corticosteroids markedly attenuates airway responsiveness to standardized exercise challenge in a dose-dependent manner.[13] With both budesonide[13] and fluticasone[14], the post-exercise decrease in FEV1 in laboratory conditions averaged <10%. In patients using these drugs in an effective and adherent manner, pre-treatment with a β2-agonist is not routinely indicated. If, however, a particular vigorous activity produces exercise-induced bronchospasm in such patients, pre-treatment with an inhaled β2-adrenergic agonist is appropriate. This may be especially important when the activity is performed in freezing or subfreezing ambient conditions (e.g. cross-country skiing).

On the other hand, if exercise-induced bronchospasm develops spontaneously during unscheduled activities in a patient taking an inhaled corticosteroid, the clinician first should evaluate inhaler technique and adherence before adding a second controller medication. If an inhaled corticosteroid is being effectively and consistently delivered at an appropriate dose, and exercise-induced bronchospasm associated with activities of daily living persist, a second controller medication is indicated. In this circumstance it is more rational to add a leukotriene modifier rather than a long-acting inhaled β2-adrenergic agonist such as formoterol (Foradil, Novartis, East Hanover, NJ) or salmeterol (Serevent, GlaxoSmithKline, Research Triangle Park, NC). This is because the pathogenesis of exercise-induced bronchospasm involves increased production of cysteinyl leukotrienes[16] and a leukotriene modifier provides sustained bronchoprotection.[15,20] The duration of protection against exercise-induced

bronchospasm (bronchoprotective effect) diminishes with regular use of inhaled salmeterol[18,19,33-36] (and presumably with formoterol as well) but not with a leukotriene modifier[4,18,19] (Figure 3). The decrease in duration of protection of long-acting β-agonists with daily use is particularly relevant to children. A dose administered at home before school may not provide protection four or more hours later. In contrast, whatever benefit is derived from a leukotriene modifier will be sustained for the entire dosing interval (Table). With montelukast, a bedtime dose provides protection throughout the next day.[20] There is no evidence that a combination of a long-acting β2-adrenergic agonist and an inhaled corticosteroid (e.g., Advair, Symbicort) provides greater protection from exercise-induced bronchospasm than corticosteroid alone.

The International Olympics Committee has approved the use of all of the above medications (i.e. inhaled corticosteroids, inhaled short-acting and long acting β2-adrenergic agonists, and oral leukotriene modifiers) for use during competition, but banned the use of oral β-adrenergic agonists,[37] because they can modestly increase muscle strength. There are no controlled studies on the efficacy of these drugs in elite winter sport athletes where the prevalence of exercise-induced bronchospasm is increased.[3] However, survey results indicate that appropriate use of these medications allow elite athletes to train and compete; several won medals at the 1998 Nagano Winter Olympics.[3]

ISOLATED EXERCISE-INDUCED BRONCHOSPASM

In patients who experience exercise-induced bronchospasm only in association with scheduled vigorous activity such as jogging several times a week, maintenance medication is not indicated. Rather, in such patients pre-treatment with 200-400 μg of inhaled albuterol 15 minutes before the activity, using optimal inhalation technique, will block exercise-induced bronchospasm in most patients.[29] Salmeterol or formoterol can be used in place of albuterol if the duration of protection from albuterol is insufficient. Because formoterol has a more rapid onset of action, a patient would only have to wait 15 minutes after taking a dose before beginning exercise compared to 30–60 minutes after salmeterol. If pre-treatment with a β2-adrenergic agonist is insufficient in patients participating in activities that produce high minute ventilation, especially in cold weather or in elite athletes, a leukotriene modifier can be added one hour or more before the activity.

Exercise-induced bronchospasm that develops from unscheduled activities of daily living can be effectively attenuated by leukotriene modifiers[15,20] or twice-daily, inhaled corticosteroids.[13,14] It is possible that once-daily inhaled corticosteroids also may be effective but controlled clinical trials have only examined the effects of twice-daily administration.

Controlled clinical trials in adults have demonstrated that pre-treatment with 2 mg inhaled cromolyn delivered by MDI (Intal, Aventis, Bridgewater, NJ),[38] or oral β2-adrenergic agonists[29] (i.e., albuterol) have minimal bronchoprotective effects. Pre-treatment with inhaled ipratropium[38] (Atrovent, Boehringer Ingelheim, Ridgefield, CT), oral ketotifen[39] (a relatively H1 selective histamine antagonist and mast cell stabilizer, not available in the United States), and most antihistamines[21,22] are ineffective in preventing exercise-induced bronchospasm. Also, it is noteworthy that maintenance therapy with inhaled albuterol, 2 puffs four times a day for only one week, paradoxically increased exercise-induced bronchospasm and decreased the post-exercise bronchodilator response to albuterol in a double-blind, placebo-controlled crossover study in adults with asthma.[40]

SUMMARY

Exercise frequently triggers symptoms of asthma in children that may cause them to abstain from certain activities. The pathogenesis involves a defect in respiratory heat exchange that probably triggers mast cell and eosinophil release of mediators, including leukotrienes. The goal for therapy is prevention of exercise-induced bronchospasm either by pre-treating the patient with isolated exercise-induced bronchospasm using an inhaled β2-adrenergic agonist before a scheduled event or treating the underlying inflammation when exercise-induced bronchospasm is part of persistent asthma. Depending upon severity, either an inhaled corticosteroid, an oral leukotriene modifier, or a combination of both may be required to prevent exercise-in-

duced bronchospasm. In some patients, pretreatment with a short-acting inhaled β2-selective agonist may still be required before a particularly vigorous activity, especially in cold, dry environmental conditions. Because of tachyphylaxis, long acting β2-adrenergic agonists have a limited role in treating exercise-induced bronchospasm.

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