Physical Activity, Asthma, and Exercise-Induced Bronchoconstriction

The United States ranks in the top tier internationally in the prevalence of asthma symptoms for both children and adults. In the United States, asthma currently affects more than 22 million people, including over 6 million children.

Asthma is characterized by chronic inflammation of the airways; this inflammatory process causes airways to narrow by increasing the amount of mucous lining the airway walls (Figure 1A), by swelling of the airway wall and by constricting the airways through contraction of the airway smooth muscle (1B). The chronic inflammation associated with asthma increases the sensitivity of the airways to "triggers" of airway constriction. Common triggers include; dust and dust mites, airborne pollution, cold/dry air, airborne pollen and mold spores, infections and high ventilation exercise. The general term for this increased sensitivity is called bronchial hyperreactivity (BHR). The airways of most people will respond in some fashion to a variety of triggers with smoke or other air pollutants resulting in varying degrees of reaction. Those diagnosed with asthma are particularly responsive to many triggers and the reactivity may vary between individuals, as well as within individuals, depending upon air quality, allergen load, and preexisting airway inflammation due to common colds, and stress levels. Persons with allergies (atopic) are typically more susceptible to airway triggers.

There is mounting evidence for a genetic influence in the development of asthma. A better understanding of the link between genetic predisposition and the effect of environmental triggers on the development of asthma will provide a path to the prevention of new-onset asthma and improved asthma treatment. For example, the single nucleotide polymorphism of Glutathione S-transferase π (GSTP1) ile105 is implicated in the development of new-onset asthma in children participating in outdoor sports in high ambient ozone, with a hazard ratio for new-onset asthma identified as 6.15 (2.2-7.4).

One hypothesis that has been advanced to explain the increase in asthma in developed countries is the hygiene hypothesis. This hypothesis suggests that our increased vigilance against infections through emphasis on avoidance of exposure to infections in children, aggressive immunization programs against
and antibiotic treatment of infectious diseases and minimization of exposure to allergens leads to an altered immune response. This appears to affect maturation of the Th-1 (normal) immune response with an increased expression of the Th-2 (atopic) response. The development of resistance or sensitivity to environmental antigens depends to a large extent on the nature of immunological memory that is generated during early antigen encounters in infancy and early childhood.26 Because the fetal and early infancy immune response is naturally skewed toward the Th-2 phenotype, a high risk window for Th-2 development is present in early age. Early exposure to infections and microbials promotes the production of Th-2 inhibitory cytokines and promotes normal immune system development.

Childhood exposure to airborne allergens and upper respiratory infections increase the probability of developing chronic asthma. The genetic predisposition for the development of an immune response to common allergens (atopy) is the strongest identifiable factor for predicting the development of asthma. Indoor and outdoor air quality plays a large role in both the development and persistence of asthma and may influence the severity of asthma. Persistent exposure to tobacco smoke, including second hand tobacco smoke and other air pollutants, results in airway irritation, chronic inflammation and the possibility of developing chronic asthma in susceptible individuals. The presence of airway hyperresponsiveness in childhood, including that triggered by exercise predicts that asthma will be present in adulthood, indicating a genetic component to the development of asthma.29 Significantly, the presence of airway hyperresponsiveness in children and adolescents who did not have asthma, combined with household exposure to furred pets increased the risk of development of adult asthma.

Obesity is an established risk factor for asthma.36 Obesity, particularly if it results in a large chest and abdominal mass, will reduce lung volume and alter the mechanical support system of the airways (Figure 1). This change in airway architecture makes the airway smooth muscle more susceptible to airway smooth muscle hyperresponsiveness. In non-obese, non-asthmatic subjects obesity-simulated increases in chest wall mass resulted in airway responsiveness to a chemical challenge that would be expected in individuals having asthma.40 The change in breathing mechanics because of the obesity may result in misdiagnosed wheeze due entirely to the obesity-derived mechanical change and not asthma. Therefore, treatment for obesity-related asthma should include a reduction in body fat. In fact, when obese asthmatics lose weight, asthma severity and symptom scores decrease.36

### Diagnosis of asthma

Chronic cough is frequently the first sign of asthma, however cough can be confused with acute upper respiratory infections, i.e. the common cold, bronchitis, or chronic obstructive pulmonary disease (COPD). Overt wheezing in response to triggers (cold/dry air, exercise or allergen exposure) is a symptom that should not be ignored. Complaints by individuals with asthma include trouble breathing and “chest tightness” or pressure in the chest, often associated with exercise or exposure to allergens.

In part, diagnosis of asthma is based on a history of breathing difficulties particularly if accompanied by “wheezing,” a high pitched whistling sound emanating from inside the chest while breathing out. Frequently a whistling sound emanating from the throat (the vocal cord) upon exhalation in particular, may indicate vocal cord dysfunction (VCD see below) and is often misinterpreted as an asthma-like wheezing. VCD may be as high as 5% of an athletic population.35 Asthma is frequently associated with a chronic cough, particularly at night and is accompanied with “tightness in the chest.” Studies have shown that in athletes, a diagnosis based on self-reported symptoms is not more accurate than a coin toss.26, 33

A definitive diagnosis of asthma is best made by including measurement of lung function in a specialized clinical laboratory in combination with clinical history. Lung function tests (commonly called “spirometry”) will show the presence of airway obstruction and, after the administration of airway-opening drugs (bronchodilators), a relief of the obstruction can often be measured. Unfortunately these tests are difficult to perform in children under the age of 6 making diagnosis in young children dependent on the presence of symptoms only. For adults and children over 6 challenge tests can be performed. The various tests are discussed in the EIB diagnosis section below.

Vocal cord dysfunction is a disorder that is frequently misdiagnosed as asthma or EIB, particularly in athletes and others who are active. VCD is a condition where the muscles of the vocal cord contract, limiting airflow through the airway. VCD typically results in a pronounced inspiratory wheeze in the upper (extra-thoracic) airway that is frequently confused with the wheeze associated with exercise-related asthma; however, the asthma-related wheeze is more commonly heard within the chest wall upon exhalation rather than inspiration, as with VCD. VCD is often comorbid with exercise-induced bronchospasm (EIB).

In a study examining 370 elite athletes, Rundell et al.36 observed inspiratory stridor consistent with VCD in 5.1% (18 females, 1 male) and the presence of EIB in 30% of the athletes, with 10 of those having EIB (52.6%) also having symptoms of VCD. VCD should be considered in athletes who have a preliminary diagnosis of asthma but are unresponsive to treatment. VCD is associated with typical changes in breathing pattern during lung function tests and is sometimes related to psychological stress.
Treatment of asthma

The National Institutes of Health convened an expert panel to develop recommendations to improve the diagnosis and treatment of asthma. The goals of treatment are outlined in Table 1. Because asthma is an inflammatory disease of the airways the inflammation must be the primary target of treatment.

Treatment should be based on the initial assessment of asthma severity and regular monitoring of the effectiveness of the treatment using patient self-assessment and spirometry. Severity is classified as “intermittent” or “persistent—mild, moderate, severe.” Intermittent asthma may be managed simply by reducing exposure to the triggers and providing medications that provide temporary relief from the asthma (see Table 2, Medications Used to Control Asthma). At the other end of the spectrum, management of severe persistent asthma may require regular use of medication, including inhaled corticosteroids, powerful anti-inflammatory medications (Table 2).

The relief of acute asthma symptoms involves the use of bronchodilator medications that result in the relaxation of the smooth muscle in the airway. These medications include the short-acting β-agonists, e.g. albuterol, pirbuterol, alone or in combination with anticholinergics, e.g. ipratropium bromide. As might be expected, long-term control of asthma requires the use of anti-inflammatory drugs, e.g. corticosteroids—budesonide, fluticasone, alone or in conjunction with leukotriene antagonists, e.g. montelukast. The decision on which drugs to use and in what dosage is based on a "stepwise” model where the short-acting drugs are used in the treatment of intermittent asthma and longer-acting, anti-inflammatory drugs are used in increasing combinations to treat persistent—mild, moderate, severe asthma. Chromolyn sodium, a drug that blocks the release of inflammatory mediators, particularly from mast cells, is used for the treatment of EIB, but rarely alone for the treatment of asthma.

Most asthma medications are delivered by inhaling the drug in fine liquid or powder form. The delivery of the drug to the parts of the lung where they are needed is critically dependent on the proper use of the inhaler; all patients should be carefully instructed on the proper use of these instruments and should be observed frequently to ensure continued proper use. The administration of beta-2-agonists by metered dose inhalers should include the use of a chamber that holds the aerosolized medication to assure optimal deposition of the medication in the lung.

Hospital or community based asthma education programs for adults, children and families are effective for increasing activity levels, reducing unscheduled health care visits and school absenteeism.7, 15 In general these educational programs should increase knowledge about asthma and the medications used to control asthma. In addition participants should learn the proper use of inhaled medicine delivery devices and how to monitor changes in asthma to recognize early signs of deterioration.

Regular physical activity alone clearly improves quality of life and fitness levels and decreases school or work-related absences and use of medications.42 Thus, regular activity should be encouraged as part of the treatment plan for asthma.

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Table 1. Goal of therapy: control of asthma

<table>
<thead>
<tr>
<th>Reduce impairment</th>
<th>Reduce risk</th>
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<tbody>
<tr>
<td>Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, in the night, or after exertion).</td>
<td>Prevent recurrent exacerbations of asthma and minimize the need for emergency doctor visits or hospitalizations.</td>
</tr>
<tr>
<td>Require infrequent use (2 days a week) of inhaled Short Acting Beta Agonists (SABA) for quick relief of symptoms (not including prevention of exercise-induced bronchospasm [EIB]).</td>
<td>Prevent loss of lung function; for children, prevent reduced lung growth.</td>
</tr>
<tr>
<td>Maintain (near) normal pulmonary function.</td>
<td>Provide optimal pharmacotherapy with minimal or no adverse effects of therapy.</td>
</tr>
<tr>
<td>Maintain normal activity levels (including exercise and other physical activity and attendance at school or work).</td>
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<tr>
<td>Meet patients’ and families’ expectations of and satisfaction with asthma care.</td>
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Adapted from National Institutes of Health, 2007. 25
Exercise-induced bronchoconstriction (EIB) and exercise-induced asthma (EIA)

The terms exercise-induced bronchoconstriction (EIB) and exercise-induced asthma (EIA) are frequently used interchangeably. A narrowing of the airways (bronchoconstriction) occurs in response to exercise in about 10% of the general population, including those with no apparent asthma, suggesting that the term EIA is inappropriate in at least some of those with exercise-related bronchoconstriction. EIB can occur in people who have no apparent asthma and in the majority of individuals with diagnosed asthma. However, the mechanism that provokes the bronchoconstriction is likely the same; athletes without asthma who experience EIB show similar post-exercise elevations of bronchoconstricting mediators as those with asthma, suggesting that this response may be an intermittent (non-persistent) asthma unique to exercise in these individuals.\textsuperscript{13, 27}

EIB most often occurs after exercise with the maximum response typically 5-15 minutes post-exercise. The bronchoconstriction generally resolves spontaneously with airway function returning to normal levels within 20 to 60 minutes after exercise. Of the three mechanisms of airway narrowing seen with asthma (Figure 1A, B) EIB involves only the narrowing of the airway through airway smooth muscle contraction. Because EIB generally resolves spontaneously medications may not be needed to reverse the narrowing. In any case, the fact that EIB involves only smooth muscle contraction means that the bronchoconstriction is readily reversed with the use of drugs that relax the smooth muscles (discussed in detail below).

Table 2. Medications to control asthma

<table>
<thead>
<tr>
<th>Relief of an acute asthma episode</th>
<th>Long-term control of asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used to provide relief from an asthma attack; also may be used to prevent an asthma attack.</td>
<td>These medications are used on an “as needed” basis to control asthma and prevent asthma attacks.</td>
</tr>
<tr>
<td>• Short-acting β-2 agonists, e.g. albuterol</td>
<td>• Inhaled corticosteroids</td>
</tr>
<tr>
<td>• Anti-cholinergics; Ipatropium, e.g. Atrovent</td>
<td>• Long-acting β-2 agonists</td>
</tr>
<tr>
<td>• In severe attacks—inhaled or oral corticosteroids</td>
<td>• Leukotriene modifiers</td>
</tr>
<tr>
<td>• Cromolyn, nedocromil</td>
<td>• Theophylline</td>
</tr>
</tbody>
</table>

Consult with your physician as needed.

Figure 1. Four mechanisms by which airways can be narrowed

A. Mucous accumulation; B. Constriction of airway smooth muscle, swelling of airway wall; C. Loss of parenchymal support, as with obesity-related decreased resting lung volume.

Diagram provided by Frank Cerny, PhD
Two hypotheses have been advanced to explain the development of EIB. EIB can be induced at rest simply by increasing ventilation to a level that mimics that measured during exercise for 5-8 minutes. Therefore, it is clear that EIB is triggered by something related to increases in ventilation rather than to something unique to exercise. One hypothesis suggests that airway dehydration during high levels of ventilation results in osmotic changes in the cells lining the airways and this triggers a release of bronchoconstricting mediators such as histamine, leukotrienes and prostaglandins that result in EIB.1 The second hypothesis proposes that cooling of the airway during high levels of ventilation leads to high levels of blood flow in and swelling of the airway upon airway rewarming during recovery from exercise;11 however, this theory does not account for the higher concentrations of bronchoconstricting mediators present during an EIB exacerbation. Thus, the evidence showing release of bronchoconstricting mediators strongly supports the osmolar hypothesis.12 Figure 2 shows the cascade of airway water loss leading to the release of bronchoconstricting mediators.

The incidence and severity of EIB is increased when exercise is performed in a cold/dry environment; conversely, incidence and severity is reduced after exercise in warm, humid conditions.21, 38 Since cold air is less humid this further suggests that airway water loss is the primary contributor to EIB.1 A study by Evans et al10 confirmed that the primary trigger to an EIB response is the dryness of the inhaled air and not the temperature; however, facial cooling during exercise in the cold can be a significant contributor to bronchoconstriction through vagal nerve influence.32 These observations support the observation that cross-country skiing results in higher incidence and severity of EIB than swimming in a heated pool area. However, a high prevalence of EIB in elite swimmers11 and children5.39 using indoor pools has been attributed to the inhalation of trichloramines, a product of chlorine interaction with nitrogen compounds such as urine and sweat in the pool water present in high concentrations in the air immediately above the water surface. Environmental factors that can interact with heat and humidity to enhance EIB include air pollutants such as sulfur dioxide, a common byproduct of coal and petroleum burning, and ozone, produced through the reaction of ultraviolet light and oxygen.17

Once EIB has occurred there may be some protection from another episode for the subsequent 2-4 hours.4, 31 The protection is greatest immediately following the first bout and decreases over the following 4 hours. There is less protection if the first exercise bout, and thus the severity of the EIB, was mild. This “refractory period” for EIB suggests that EIB involves the release of certain stimuli (mediators) that may become depleted during the first bout of exercise, thus reducing the possibility of a second EIB episode until these mediators can be replenished.

EIB occurs in up to 90% of those with asthma and in about 35% of those with allergies and no asthma,18 and in up to 50% of certain athletic groups.34 The prevalence of EIB among elite runners is slightly higher than that estimated for runners and has been attributed to an allergic response. The high prevalence reported for elite swimmers (20-30%)1.14 have been related to airway oxidative stress from inhalation of trichloramines in indoor swimming pools. The high ventilation of cold dry air during competition and training, as well as “training through” a respiratory infection has been suggested as causal to the high (20-50%) prevalence identified in Nordic skiers.34, 36 Asthma and EIB among ice rink athletes has been reported to be extremely high (25%-40%).34, 35 The likely candidate for this response is the high ventilation of combustion-derived fine and ultrafine particulate matter emitted from ice resurfacing machines. Rundell34 noted a decline in resting lung function in elite hockey players after training in rinks high in pollutants that was similar to that identified in heavy smokers. It has been suggested that inhalation of combustion-derived particles during exercise creates high oxidative stress in the airways and results in antioxidant depletion and lipid peroxidation. Recent studies have related new onset asthma to ozone exposure during outdoor sport participation.17

A 6-fold increased risk of developing new onset asthma was shown for children with the Glutathione-S-transferase single nucleotide polymorphism homozygous for isoleucine (at codon 105) that participated in youth sports in high ozone areas. These studies suggest a clear risk for the development of asthma and EIB from sport participation in harmful environmental conditions.

**Diagnosis of EIB**

As with asthma, EIB should be suspected when someone consistently complains of shortness of breath, cough, chest tightness or overt wheezing after exercise. However, a differential diagnosis to exclude alternate diagnoses such as VCD, exercise hyperventilation, exercise-induced hypoxemia, paroxysmal atrial tachycardia and other abnormalities should be done (see figure 3 for diagnostic algorithm). Because self-reported symptoms are less reliable in predicting EIB, especially in elite athletes28, 33 a differential diagnosis with spirometry and an appropriate challenge test should be done. The International Olympic Committee requires an objective test of EIB if athletes wish to use common bronchodilator medications prior to competition.

The most common tests used to diagnose EIB require the patient to increase their ventilation for a 5-10 minute period either through exercise or a voluntary increase in ventilation at rest; chemicals that are known to induce bronchoconstriction also may be used (see below). In any case pulmonary function tests (PFTs) are performed prior to the challenge test and for a period of up to 30 minutes after the challenge. PFTs measure the patient’s ability to forcefully exhale air from a fully inflated lung to complete voluntary exhalation. From this maneuver the Forced Vital
Capacity (FVC) and Forced Expired Volume in one second (FEV₁) are measured. A decrease in FEV₁ of greater than 15% after the challenge is required for a positive diagnostic test.

The standard laboratory test for diagnosis of EIB has been treadmill exercise or exercise on a cycle ergometer at an intensity that will elicit 80%–90% of the maximum estimated heart rate for 6-7 minutes; the test should include inhalation of dry air from a gas cylinder during the exercise. Lung function is measured before and typically at 5-minute intervals for 20 minutes after exercise to detect a decrease in the ability to forcefully breathe out. The high exercising heart rate will elicit a level of ventilation sufficient to stimulate bronchoconstriction in most, but not all, who experience EIB. Non-exercise tests that can be used to diagnose EIB include eucapnic voluntary hyperpnea (EVH)—breathing at a level equivalent to 80% of the subject’s maximum voluntary ventilation for 6 minutes. Decreases in blood CO₂ levels during EVH are prevented by breathing a gas mixture of 21% O₂, 5% CO₂ with a balance of N₂. EVH identifies EIB with greater sensitivity than exercise provocation tests while chemical tests have a lower sensitivity.³²

While attractive because of its potential for diagnosing EIB in real-life situations, testing in the field is not as sensitive as either laboratory exercise testing or the EVH test.⁸, ³², ³⁷ This lack of sensitivity of field tests is likely due to the highly variable environmental conditions in the field and the inability to control the level of ventilation over the required 6-7 minute period.

Because of its high sensitivity and objectivity the EVH test is currently the recommended test by the International Olympic Committee for the diagnosis of EIB.² Once EIB has been verified through objective testing the athlete may be cleared to use β-agonists (Table 2) for the treatment of their EIB.

Other challenges may involve the inhalation of chemicals, e.g. methacholine, inhaled powder mannitol, adenosine, known to elicit bronchoconstriction in susceptible individuals (Figure 2). The methacholine test, a test that acts directly on airway smooth muscle constricting receptors, involves breathing in nebulized methacholine in increasing doses until a 20% fall in forced expiratory volume in one second (FEV₁) occurs. Then a PC₂₀ (provocative concentration which causes this 20% decrease in

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Figure 2. Cascade of airway water loss leading to the release of bronchoconstricting mediators involved in EIB

Bars on left indicate the challenges available to stimulate possible pathways.

Adapted from O’Byrne, et al. 2009. ²⁶
FEV\(_1\)) or PD\(_{20}\) (provocative dose) is calculated. Methacholine is a direct test that is not very sensitive or specific to EIB and only measures the reactivity of the airway smooth muscle. A more appropriate alternative challenge is inhaled powder mannitol; this is an indirect challenge that acts similar to exercise in that it is an osmotic challenge and causes the release of bronchoconstricting histamine, prostaglandins and leukotrienes in those individuals with airway inflammation. It is a simple test that involves breathing in increasing doses of powder mannitol followed by lung function tests after each dose. The test is terminated after a 15% fall in lung function or completing the dosing scheme. As with methacholine, a PD\(_{15}\) (dose at which a 15% fall in FEV\(_1\) occurs) is calculated.

Control of EIB

Long-term control of EIB is only as good as the long-term control of the asthma. Frequent or severe EIB suggests that long-term control medications should be initiated or stepped up (see above; Table 2). Most patients are able to prevent EIB for 2-3 hours by using short-acting inhaled \(\beta\)-2 agonists prior to exercise. The long-term daily use of \(\beta\)-2 agonists to control EIB is discouraged as their effectiveness decreases over time. Leukotriene antagonists are more limited in effectiveness in preventing EIB than short-term \(\beta\)-2 agonists.\(^{19,30}\) However, recent research suggests that leukotrienes are primary mediators in air pollution-induced EIB and may be particularly effective with the ice rink athlete suffering from EIB.

Those diagnosed with EIB may have to avoid exercise under certain environmental conditions, e.g. extreme cold or high altitude. Facemasks that enhance humidification and warming of inhaled air are effective in limiting EIB in some exercisers, but may limit ventilation because of increased airway resistance.\(^6\)

The refractory period for EIB has prompted the suggestion that appropriate warm-up may minimize the possibility of EIB during subsequent exercise, but this has been difficult to substantiate. Since exercise less than 2 minutes rarely stimulates EIB and since exercise longer than 8 minutes results in a refractory period, a warm-up consisting of 2 minutes of exercise of increasing intensity, separated by 2 minutes of rest until a total of 10 minutes of exercise has been accumulated may reduce the incidence of EIB. In any case warm up consisting of exercise intervals separated by rest intervals, either alone, or combined with pre-exercise treatment can minimize the occurrence of EIB in some.\(^{23}\)

There is increasing evidence that modifications in diet may influence the severity of asthma, including EIB.\(^{24}\) Because of their potential anti-inflammatory actions reductions in dietary salt, supplementation with fish oil or increasing intake of a variety of antioxidants (Vitamin C, \(\beta\)-Carotene, lycopene and whey protein) may attenuate, but not eliminate EIB.

Regular exercise may attenuate EIB or increase the exercise level at which EIB occurs in most, but not all with asthma. It is important to note that asthma in general and EIB in particular should not prevent participation in regular physical activity, including sports.\(^{40,42}\) Intentional regular exercise training improves the quality of living, reduces EIB severity and may reduce the need for medical control of asthma.\(^{10}\)

Summary

Asthma is an inflammatory disease of the airways that results in intermittent airway narrowing due to mucous accumulation, swelling of the airway wall and constriction of the airway smooth muscles (bronchoconstriction). Diagnosis of asthma and EIB should include spirometry and challenge test(s) as symptoms alone are poor diagnostic tools. Treatment involves control of the inflammatory process with inhaled corticosteroids and of smooth muscle constriction with \(\beta\)-2 agonists. The intermittent narrowing may be triggered by a number of factors, including allergens and exercise. Exercise-induced bronchoconstriction involves only the constriction of the bronchial smooth muscles and is therefore very treatable, both in terms of prevention and reversal. EIB appears to be stimulated by loss of fluid from the airway during periods of high ventilation, whether at rest or during exercise. EIB incidence and severity are enhanced by exercising in cold, dry environments (winter sports) or in harsh chemical environments (swimming in chlorinated pools). EIB can be minimized by ensuring optimal treatment of the underlying inflammatory process, by pre-treating with bronchodilators, by appropriate exercise warm-up and by regular exercise training.

“Because asthma in general and exercise-induced bronchoconstriction in particular are readily treated with medication, those who are diagnosed with asthma should not be discouraged from participating in regular activity but should be encouraged to be active as part of the treatment of asthma.”
For a more detailed algorithm see American Academy of Allergy, Asthma and Immunology (AAAAI) Practice Parameter for Diagnosis of EIB, 2011.

**Figure 3. Algorithm used to diagnose exercise-induced bronchoconstriction (EIB)**
References


