Practice Parameter

Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: a practice parameter

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These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology. The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing "Pathogenesis, Prevalence, Diagnosis, and Management of Exercise-Induced Bronchoconstriction: A Practice Parameter." This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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Published Practice Parameters of the Joint Task Force on Practice Parameters for Allergy & Immunology include the following:

1. Practice parameters for the diagnosis and treatment of asthma. *J Allergy Clin Immunol.* 1995;96(suppl):S707–S870.
2. Practice parameters for allergy diagnostic testing. *Ann Allergy.* 1995;75:543–625.
3. Practice parameters for the diagnosis and management of immunodeficiency. *Ann Allergy.* 1996;76:282–294.
4. Practice parameters for allergen immunotherapy. *J Allergy Clin Immunol.* 1996;98:1001–1011.
5. Disease management of atopic dermatitis: a practice parameter. *Ann Allergy.* 1997;79:197–211.
6. The diagnosis and management of anaphylaxis. *J Allergy Clin Immunol.* 1998;101(suppl):S465–S528.
7. Algorithm for the diagnosis and management of asthma: a practice parameter update. *Ann Allergy.* 1998;81:415–420.
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11. Disease management of drug hypersensitivity: a practice parameter. *Ann Allergy.* 1999;83(suppl):S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. *Ann Allergy.* 2000;85(suppl):S521–S544.
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CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE

Category of evidence

Ia Evidence from meta-analysis of randomized controlled trials
Ib Evidence from at least 1 randomized controlled trial
IIa Evidence from at least 1 controlled study without randomization
IIb Evidence from at least 1 other type of quasi-experimental study
III Evidence from nonexperimental descriptive studies, such as comparative studies
IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

Strength of recommendation

A Directly based on category I evidence
B Directly based on category II evidence or extrapolated recommendation from category I evidence

C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
LB Laboratory based

GLOSSARY

Exercise-induced bronchoconstriction (EIB) is defined as a transient narrowing of the lower airway following exercise in the presence or absence of clinically recognized asthma. The term *exercise-induced asthma* (EIA) is not used in this document because it may imply incorrectly that exercise causes rather than exacerbates or triggers an attack of asthma.

Bronchial hyperresponsiveness (BHR) is an increase in sensitivity to an agent and is expressed as the dose or concentration of a substance that produces a specific decrease in forced expiratory volume in 1 second (FEV_1) (eg, provocation dose or provocative concentration causing a decrease of 20% [PD_{20} or PC_{20}, respectively]).

Bronchial reactivity is the rate of change of the FEV_1 in relation to the dose or stimulus (eg, response dose ratio [RDR] with mannitol is the percentage decrease divided by the dose that achieves that decrease or the percentage decrease in exercise in response to the optimal stimulus).

Conditioning is defined as preparing the body for physical exercise and, in particular, sports performance.

Competitive athletes are individuals who engage in strenuous aerobic activity at any level from grade school age and older.

Elite athletes are highly competitive individuals who train and compete consistently at higher levels (eg, Olympics, professional aerobic sports).

Tolerance is a decrease in the degree and/or duration of response to an agent when used continuously instead of intermittently. Tolerance ordinarily refers to the inhibition of bronchoconstriction and in some cases bronchodilation to β_2-adrenergic agents.

PREFACE

The goal of "Pathogenesis, Prevalence, Diagnosis, and Management of Exercise-Induced Bronchoconstriction: A Practice Parameter" is to empower health care specialty practitioners to provide outstanding health care services to their patients in diagnosing and managing EIB. This practice parameter is designed to accomplish this goal by providing the most up-to-date, evidence-based information and recommendations on the diagnosis and management of EIB. The term *EIA* is not used in this document because it implies a condition that does not exist—that of exercise that induces asthma. Instead, the term *EIB* is used throughout, and EIB is further differentiated based on whether the patient has chronic asthma in which exercise triggers bronchoconstriction or the patient does not have chronic asthma and only has bronchoconstriction associated with exercise.

This document was developed by a Workgroup under the aegis of the Joint Task Force on Practice Parameters. Three national allergy and immunology organizations—the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI)—have authorized the Joint Task Force to develop new parameters and update existing parameters. To date, the Joint Task Force has developed and published 28 practice parameters, including some that have been updated, for the specialty of allergy/immunology (see www.jcaai.org).

This parameter is the first such parameter for EIB. It provides the latest in evidence-based recommendations on the pathogenesis, prevalence, clinical presentation, diagnosis, differential diagnosis, and treatment (both nonpharmaceutical and pharmaceutical) of patients having or suspected of having EIB, with or without chronic asthma, in recreational and elite athletes and nonathletes. The document was written, edited, and reviewed by specialists in the discipline of allergy/immunology and was exclusively funded by the allergy and immunology organizations noted above.

The Workgroup, chaired by John M. Weiler, MD, MBA, developed the initial draft, which was then edited and reviewed by the Joint Task Force. In the development of this document, a comprehensive search of the medical literature was performed using the PubMed MEDLINE search engine and included Cochrane databases. Searches used keywords that were associated with EIB. Workgroup members, all of whom were experts in the area of EIB, contributed additional manuscripts to the list. Published clinical investigations were rated by category of evidence and the strength of clinical recommendations. After the Joint Task Force completed its review and editing of the manuscript, subject matter experts in the field of allergy and immunology and EIB were recruited to review the manuscript. These expert reviewers were appointed by the AAAAI and ACAAI. The authors of the document then diligently reviewed and evaluated additional comments and suggestions from these reviewer experts. The revised final document presented here was approved by the sponsoring organizations and reflects an evidence-based and generally accepted consensus parameter on the diagnosis and management of EIB encompassing the most contemporary evidence-based understanding of the pathogenesis, prevalence, clinical presentation, diagnosis, differential diagnosis, and treatment (both nonpharmaceutical and pharmaceutical) of patients having or suspected of having EIB, with or without chronic asthma, in recreational and elite athletes and nonathletes.

The term *EIB* is defined as a transient narrowing of the airway with increasing airway resistance after exercise. Exercise-induced bronchoconstriction most likely occurs because of dehydration of the airway resulting in a hyperosmolar environment, leading to mast cell mediator release and subsequent bronchoconstriction. The hyperosmolar theory of the pathogenesis of EIB is described in this document as the leading theory for EIB. The document also provides evidence that as many as 90% of asthmatic patients and 50% of competitive athletes may experience EIB. The diagnosis of

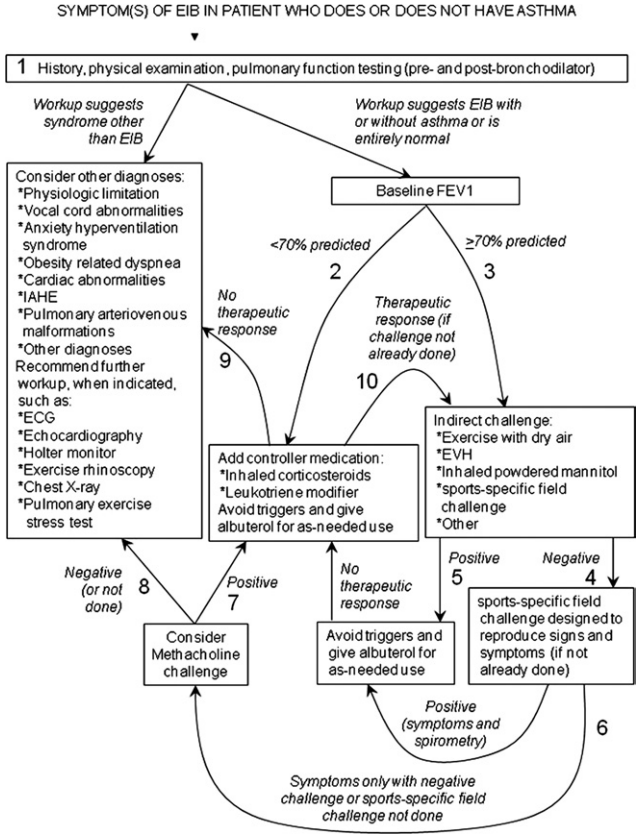

Figure 1. Algorithm: The major decision tree for the evaluation and management of individuals with suspected EIB in the presence or absence of chronic asthma.

EIB, which relies optimally on objective pulmonary function testing and exercise challenge, is discussed, as is the clinical presentation and specifics of diagnosis (eg, the value and conduct of exercise challenge or surrogate challenges). The differential diagnosis is elucidated, including other upper and lower airway disorders, cardiopulmonary conditions, and other diseases and conditions that mimic EIB. Finally, therapy is discussed, including the use of bronchodilators, anti-inflammatory agents, and the combination of pharmacotherapy and nonpharmacotherapy (eg, warm-up and cool-down maneuvers and dietary intervention). The diagnosis and particularly the management of EIB in elite athletes are discussed in detail in a separate section to explain how this condition may affect these highly conditioned individuals. Tables and figures are provided to illustrate key points.

The Executive Summary details the key items in summary statements in the Practice Parameter. The Executive Summary does not discuss all of the parameter topics in depth. An annotated algorithm in the document provides the major decision tree for the evaluation and management of individuals with suspected EIB in the presence or absence of chronic asthma (Figure 1). This is followed by a list of summary statements that provide the key points in the evaluation and management of EIB. In the evidence-based commentary, the summary statements are repeated and are then followed by text that elaborates and supports each summary statement. The evidence-based commentary first discusses the general issues relating to EIB including pathogenesis, prevalence, clinical presentation, diagnosis, differential diagnosis, and treatment (both nonpharmaceutical and pharmaceutical) of patients having or suspected of having EIB, with or without chronic asthma, in recreational and elite athletes and nonathletes.

The Joint Task Force on Practice Parameters expresses gratitude to the AAAAI, ACAAI, and JACAAI, who provided support for the development of the parameter, and to the individuals who have dedicated time and effort to the drafting and review of this document.

ALGORITHM

Annotations for Algorithm

1

History, physical examination, and pulmonary function tests pre and postbronchodilator (with flow volume loops, and pre/postbronchodilator functions) are necessary if there is suspicion of asthma or EIB. History alone should not be used to diagnose or exclude the diagnosis of EIB. If pulmonary function equipment (i.e., spirometry) is not available in the clinic setting, patients should be referred to a pulmonary function laboratory or to a physician with office spirometry equipment. Peak flow is a poor surrogate for diagnosis.

2 and 3

Expert consensus is, if baseline FEV_1 is 70% predicted value, exercise challenge with dry air and EVH should not be done for safety reasons. Other challenges (e.g., exercise without the use of dry air, mannitol) should be performed with caution if baseline FEV_1 is 70% predicted value.[3] Eucapnic voluntary hyperpnea may be a surrogate for exercise, especially for those who cannot exercise or for elite athletes; however, EVH can elicit a severe response. Inhalation of dry air as part of the exercise protocol is strongly recommended to diagnose or exclude EIB because it increases sensitivity to the challenge. Mannitol challenge is currently approved in 23 countries including the US. More than one indirect challenge may be required for diagnosis if a first challenge is negative. When predicted spirometry values are obtained outside of the range of the algorithm, judgment must be used when interpreting the results. Care must be taken when evaluating patients who are unusually tall or short, in particular, and have a predicted FEV_1 that is 70%.

4

If indirect challenge is negative, then a field challenge to reproduce signs and symptoms of the exercise-induced bronchospasm is recommended.[3]

5

If indirect challenge is positive, therapy with albuterol as needed with avoidance of triggers for EIB may be indicated.

6

If field challenge is negative but the patient is still symptomatic, a methacholine challenge may be performed to rule out BHR.

7

If methacholine challenge is positive, controller medications, including inhaled steroids, should be considered for probable asthma in conjunction with avoidance of triggers and use of albuterol as needed.

8

If methacholine challenge is negative, a different diagnosis should be considered. An extensive differential diagnosis should be considered if the evaluation (including history, physical examination, pulmonary function testing pre and postbronchodilator, exercise challenge, and methacholine) is not consistent with EIB. The differential diagnosis encompasses physiologic limitations including VCD, exercise dyspnea, anxiety, obesity or a gradient of poor conditioning, or cardiac abnormalities (e.g., tachycardia, idiopathic hypertrophic subaortic stenosis, hyperventilation syndrome, pulmonary artiovenous malformation). The further evaluation may include ECG, echocardiography, Holter monitor, and exercise rhinoscopy as indicated.[2,3]

9

If the controller medication is ineffective, then the steps described in Annotation 8 should be followed.

10

If the controller medication is effective, challenge should be performed to document EIB if the FEV_1 after controller therapy is greater than 70%. If the FEV_1 is not greater than 70%, additional consideration should be given to different diagnoses.

EXECUTIVE SUMMARY

Introduction and Definition (Summary Statement 1)

Exercise-induced bronchoconstriction is defined as the transient narrowing of the lower airways that occurs after vigorous exercise.[1–4] Exercise-induced bronchoconstriction may be observed in patients who have or do not have chronic asthma based on spirometry.[1–8] The term *EIA* should no longer be used because exercise does not induce asthma but rather is a trigger of bronchoconstriction. The diagnosis of EIB usually requires a decrease in FEV_1 after exercise of 10% to 15% of the preexercise value.[3,6–8] Exercise-induced bronchoconstriction is a manifestation of BHR and is often the first sign of asthma.[3,6–8] A β_2-agonist by inhalation is the most widely used treatment given immediately before exercise to prevent EIB.[7] Within 12 weeks of initiating daily treatment with inhaled corticosteroids (ICS) alone, the inflammation and resulting decrease in pulmonary function are attenuated in some but not all patients who have EIB with asthma.[7–9]

Pathophysiology of EIB (Summary Statements 2–7)

The pathophysiology of EIB has been elucidated during the past decade and a half. Exercise, especially strenuous exercise, causes hyperpnea, which in turn causes drying of the airways, requiring humidification and often warming of large volumes of air during a short interval. The respiratory water loss that occurs at high ventilation rates, which may be associated with airway cooling and dehydration, leads to increases in osmolarity of the airway surface. The increase in osmolarity of the airway is postulated to induce degranulation of airway mast cells with release of chemical mediators, including prostaglandins (PGs), leukotrienes (LTs), and histamine, with bronchoconstriction of the airways. Inflammation of the airway may occur with the involvement of lymphocytes, eosinophils, epithelial cells, and perhaps neutrophils.[10–13] This is the predominant explanation for EIB called the *osmotic theory*.[10–13] The most important determinants of the EIB response and its severity are the water content of the inspired air and the level of work that is achieved and sustained during exercise.[12] It is important to understand that exercise itself is not necessary to cause the airways to narrow as demonstrated by the ability of eucapnic voluntary hyperpnea (EVH) of dry air to induce bronchoconstriction, similar to what is observed after exercise.[10–13]

It was previously postulated that warming the airway after inhalation of cold, dry air was the main mechanism causing EIB, called the *thermal theory*[10–13]; however, it is now known that cooling and rewarming of the airways are not required to provoke airway narrowing, in contrast to drying and osmotic changes with release of mediators of inflammation, which are required. It is now thought that airway rewarming may play at most only a limited role in the pathogenesis of EIB.[10–13]

In approximately half of patients who have EIB, there is an interval of refractoriness lasting approximately 1 to 3 hours immediately after an episode of EIB during which additional exercise results in little or no bronchoconstriction. This is called the *refractory period* and may also occur after strenuous exercise at a level that does not provoke EIB. This offers a nonpharmacologic approach to prevent attacks of EIB in athletes before competition.[10–13]

Genetics and Environment (Summary Statements 8–10)

It has been postulated that both genetics and the environment may contribute, together or alone, to the EIB phenotype.[14–16] Unfortunately, there is limited information at present on the genetic makeup of individuals who have EIB, whether in the presence or absence of chronic asthma. Future genome-wide association studies should clarify the role of genetics in causing the EIB phenotype.[14–16] In contrast, data exist to demonstrate that environmental conditions play an important role in some individuals in facilitating the occurrence of EIB. The environment in which training or participation occurs may contain allergens and/or pollutants that, when inhaled, are associated with oxidative stress, which may in turn enhance the development and severity of EIB.[7,10–12,14–16] This is particularly true in elite athletes in whom the pathogenesis of EIB may relate to effects on the airway developing from conditioning large volumes of dry air over months or years of training with or without exposure to environmental irritants, allergens, and infectious agents.[7,10–12,14–16]

Prevalence (Summary Statements 11–16)

Exercise-induced bronchoconstriction is reported to occur in as many as 90% of asthmatic patients,[3,6–13] perhaps as a reflection of underlying asthma. Patients with more severe or poorly controlled asthma are more likely to manifest EIB than patients with less severe or well-controlled disease.[3,6–13] The true prevalence of EIB in the general population is poorly defined; most epidemiologic studies of EIB have not differentiated asthmatic from non-asthmatic populations.[1–3,7] In addition, prevalence data are affected by the lack of consensus on how a challenge is to be performed and what constitutes a positive response.[1–3,6,7,17,18] Other factors determining prevalence of EIB in the general population include the environmental conditions, type of exercise, and intensity with which the exercise or surrogate challenge is performed.[1–3,6,7,17,18] The prevalence of EIB may also be influenced by age, sex, and ethnicity. It has long been observed that the prevalence of EIB in elite athletes appears to be higher than in the general population and depends on the environmental conditions in which exercise is performed, the type of sport, and the maximum exercise level.[1–3,6,7,17,18]

In reviewing data on the prevalence of EIB, it is important to recognize that the response to exercise in an unselected population forms a normally distributed curve, with some individuals even having increases in FEV_1 after the challenge; there is no specific cutoff that clearly distinguishes a positive from a negative test result.[1–3,6,7,17,18] It is also important to recognize that symptoms are poor predictors of individuals who will have a positive exercise challenge because so many other conditions may occur that may be confused with EIB.[1,2,7,19]

Diagnosis (Summary Statements 17–23)

Symptoms of EIB include cough, wheeze, chest pain primarily in children or chest tightness, shortness of breath, dyspnea, excessive mucous production, or feeling out of shape when the patient is actually in good physical condition.[1,2,7,17,20] These symptoms also occur with other conditions so that diagnosis of EIB based only on symptoms lacks sensitivity and specificity to predict a positive exercise challenge. The diagnosis of EIB should never be made based on symptoms alone when unaccompanied by data from an objective exercise or surrogate challenge.[1–3,6,7,17,18]

Diagnostic challenges are of 2 types: (1) direct challenges in which a pharmaceutical agent such as methacholine or histamine is the provoking agent that acts directly on airway smooth muscle and (2) indirect challenges in which exercise or a surrogate, such as EVH, inhalation of mannitol, inhalation of adenosine monophosphate (AMP), or inhalation of hypertonic saline, is the provoking agent that triggers mediator release. Mediator release in turn leads to bronchoconstriction. Indirect challenges are more specific in reflecting BHR because of airway inflammation and are preferred as a way to confirm underlying asthma.[1–3,6,7,17,18] In addition, indirect challenges are recommended for monitoring asthma therapy because BHR is most often associated with inflammation,[1–3,6,17,18] which is diminished by ICS therapy.[7–9,18]

Direct challenges using methacholine, an approved agent, may be performed in an office setting by trained personnel. The challenge, described in a consensus statement by the American Thoracic Society (ATS),[6] requires administering increasing concentrations of methacholine by inhalation and following FEV_1 levels after each dose. Drug is administered using a nebulizer and either a dosimeter with a forced inhalation from end expiratory volume or alternatively by using tidal breathing over a timed interval. A decrease in FEV_1 of more than 20% from baseline is regarded as a positive challenge result. This is documented as the PC_{20}. A PC_{20} of greater than 16 mg/mL is interpreted as normal or lack of BHR, between 4.0 and 16 mg/mL is interpreted as borderline BHR, between 1.0 and less than 4 mg/mL is considered positive with mild BHR, and less than 1.0 mg/mL is considered positive with moderate to severe BHR. Although the direct challenge is used as a screening test for chronic asthma, especially to rule out asthma, it is not useful to detect EIB because it has low sensitivity for EIB because it reflects the effect of only a single agonist.[3,6,7,18]

Indirect challenges should also be conducted only by trained personnel and using standardized protocols. For example, laboratory-based exercise should be performed as described in the consensus statement published by the ATS.[6] Such a laboratory challenge controls minute ventilation and water content of inhaled air.[3,6,7,18] Exercise should be for 6 to 8 minutes, at 20°C to 25°C, while breathing dry air at 80% to 90% of estimated maximal heart rate (HR_{max}) as a surrogate for more than 40% of maximum voluntary ventilation (MVV).[3,6,7,18] Maximal heart rate may be estimated using the formula 220 − age (in years); however, a more accurate equation, which was published recently, to predict HR_{max} is $208 - 0.7 \times$ age.[3,6,18] Ideally, the exercise ventilation should be above 60% of predicted maximum (ie, greater than 21 times FEV_1)[3,6,18]; very well-conditioned individuals may require the exercise intensity to be above a 90% HR_{max}. A recent investigation in children reinforces the need to reach a target HR_{max} of 95% for children 9 to 17 years of age; in that study, the decrease in FEV_1 was 25.1% at 95% HR_{max} but 8.8% when the children reached only 85% HR_{max} (Figure 2).[17]

Spirometry should be performed at baseline, before exercise challenge, and at predetermined times after exercise, usually at 5, 10, 15, 30, and occasionally 45 to 60 minutes after exercise. The goal is to determine FEV_1 without having the patient perform full forced vital capacity (FVC) maneuvers to avoid causing the patient to become tired by the spirometry efforts. The International Olympic Committee Medical Commission (IOC-MC) Independent Panel on Asthma recommends that FEV_1 should be recorded beginning as soon as 3 minutes after completion of the challenge to overcome the problem of posttest respiratory fatigue. A preexercise value is obtained by performing a full FVC maneuver at baseline.[3,6,7,18] A 10% or greater decrease in FEV_1 from the preexercise value at any 2 consecutive time points within

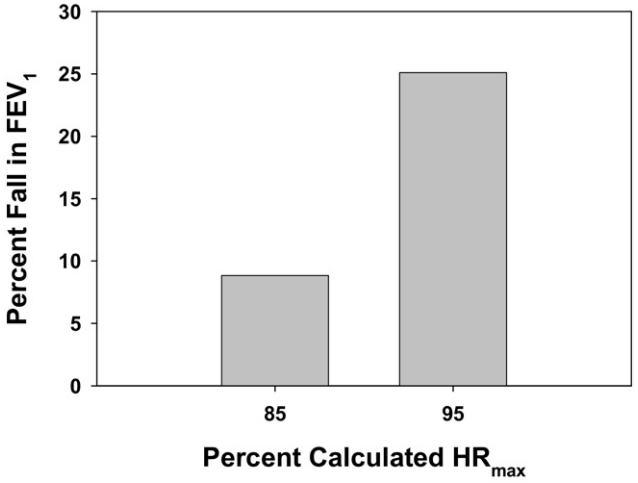

Figure 2. Exercise challenge of 20 asthmatic adolescent patients at 85% of estimated calculated maximum heart rate (Hr_{max}) resulted in only 9 of 20 testing positive for exercise-induced bronchoconstriction (mean decrease in forced expiratory volume in one second [FEV_1] of 8.84%); however, all 20 asthmatic patients tested positive after exercise at 95% of HR_{max} (mean decrease in FEV_1 of 25.11%). Adapted from Carlsen et al.[17]

30 minutes of ceasing exercise may be considered diagnostic of EIB.[3,6,7,18] It is preferable to perform FEV_1 testing after exercise without full FVC maneuvers to avoid fatiguing the patient.[3,6,7,18] If a greater decrease in FEV_1 is required such as a decrease of 25% in FEV_1 as in some pharmaceutical studies, then only 1 time point may be necessary to be diagnostic of EIB. The area under the curve (AUC) of FEV_1 should be examined to determine whether the fall is consistent and not an artifact of an inadequate spirometry effort at 1 or more time points.[3,6,7,18]

However, there is no single test that will identify all individuals who have EIB.[7] Decreases in FEV_1 that are consistent with EIB may occur in individuals who are subsequently found to have other conditions.[7] The FEV_1/FVC ratio may be useful for diagnosis of vocal cord dysfunction (VCD). A flat inspiratory loop on the flow volume curve may also suggest upper airway dysfunction rather than EIB.[7]

Exercise challenge by treadmill is most easily standardized for office practice or a hospital laboratory. Alternative exercise challenges using cycle ergometry may be more difficult to perform and may be less standardized than the treadmill challenge. Similarly, field challenge and free running are even more difficult to standardize.[3,6,7,18]

Although sport governing bodies require specific cutoff values to diagnose EIB, there is no specific decrease in FEV_1 and there is no single absolute cutoff for a decrease in FEV_1 or change in some other spirometry measure that clearly and unequivocally distinguishes between EIB and lack of EIB.[7] The ATS has suggested that the postexercise decrease in FEV_1 required to make the diagnosis must be 10%, whereas other groups have suggested a decrease of 13% to 15% is necessary to make the diagnosis.[3,6,18] A decrease in FEV_1 of 15% after a "field" challenge and a decrease of 6% to 10% in the laboratory have also been recommended.[3,6,7,18]

Surrogate challenges for exercise in which a hyperosmolar agent, mannitol, or EVH are used are increasingly being recommended by organizations that regulate drug use by elite athletes. Eucapnic voluntary hyperpnea should only be performed by highly trained specialists, and all safety precautions should be observed. Eucapnic voluntary hyperpnea may cause substantial decreases in FEV_1 in a patient with impairment caused by airway inflammation; the EVH test should be performed with caution, especially in patients with an FEV_1 that is below 80% of predicted, and should not be performed on patients in whom the FEV_1 is less than 70% of predicted.[3,6,7]

Differential Diagnosis (Summary Statements 24–33)

A variety of conditions may mimic EIB. Exercise-induced laryngeal dysfunction (EILD), primarily VCD and other glottic abnormalities, can be clearly differentiated from EIB. An exercise challenge in which a fiberscope is introduced while the exercise is being performed will provide evidence for the anatomical disorder responsible for EILD. Loud inspiratory stridor is the characteristic hallmark of EILD and is rarely seen with EIB. Flattening of the inspiratory loop on a flow volume curve also suggests EILD rather than EIB. Failure to respond to asthma management, especially treatments that prevent or treat EIB, strongly suggests consideration of another diagnosis, such as EILD.[7,19,20]

Some conditions are more difficult to differentiate from EIB with known asthma, and these conditions may be diagnoses of exclusion. Exercise-induced dyspnea and hyperventilation may simulate asthma and EIB, especially in children and adolescents.[19,20] Exercise-induced dyspnea is seen as a physiologic limitation in otherwise healthy individuals or in obese individuals without bronchoconstriction. Shortness of breath with exercise may be caused by underlying pulmonary dysfunction unrelated to EIB, for example, restrictive lung physiology caused by obesity, skeletal defects (eg, pectus excavatum), diaphragmatic paralysis, and interstitial pulmonary fibrosis. Shortness of breath accompanied by pruritus and urticaria, particularly after ingestion of certain foods such as celery, may be caused by exercise-induced anaphylaxis (EIAna). Dyspnea with exertion, with or without chest pain, may be related to cardiovascular, pulmonary, or gastroenterologic causes other than asthma and may require referral to a cardiologist, pulmonologist, or gastroenterologist. Rarely, mitochondrial enzyme deficiency with myopathy may need to be differentiated from EIB.[7,19,20] Finally, psychological factors should be considered in the differential diagnosis of EIB.[19,20]

Therapy Overview (Summary Statements 34–37)

Exercise-induced bronchoconstriction in a patient with chronic asthma suggests inadequate control of the underlying asthma or a wrong diagnosis.[7,21,22] If the diagnosis of EIB can be confirmed, anti-inflammatory therapy should be maximized until control is observed.[7,21,22]

Many pharmacotherapeutic agents are effective for the prophylaxis or attenuation of EIB even though these agents differ in their mechanisms of action and overall effectiveness. In addition, there is both intrapatient and interpatient variability in the ability of the agents to prevent or control EIB when it occurs. These agents may differ in effectiveness over time because of variability of the underlying asthma, environmental conditions, intensity of the exercise stimulus, and the potential of each agent for tachyphylaxis.[7,21–27]

β_2-Adrenergic Receptor Agonists (Summary Statements 38–41)

Short-acting β_2-agonists (SABAs), when administered by inhalation 5 to 20 minutes before exercise, depending on the agent, are effective for 2 to 4 hours in preventing EIB when used intermittently.[7,21,22] Long-acting β_2-agonists (LABAs), when administered by inhalation about 30 minutes before exercise, depending on the agent, are effective for as long as 12 hours in preventing EIB when used intermittently.[7,21,22]

Inhaled SABAs are the single most effective agents to protect against EIB when given prophylactically immediately before exercise and to accelerate recovery of FEV_1 to baseline when administered after a decrease in FEV_1 after exercise. Short-acting β2-agonists will attenuate or protect against EIB in most patients.[7,21,22,24] Their effectiveness may relate in large part to their action as functional agonists acting directly on bronchial smooth muscle (BSM) muscle receptors and by inhibition of mast cell mediator release.[21,22]

Unfortunately, regular daily use of SABAs and LABAs results in relative loss of efficacy of the agents defined as tachyphylaxis, even when used in combination with ICS.[7,21–27] Tolerance may be manifested as a reduction in duration and/or magnitude of protection against EIB when LABAs or SABAs are given before exercise and a prolongation of the time necessary for recovery from an attack of EIB when SABAs are given after exercise.[7,21–27] Therefore, because of these potential concerns of tolerance, SABAs and LABAs are recommended for use only on an intermittent (ie, less than daily) basis as absolutely necessary for prophylaxis and treatment.[7,21–27]

Long-acting β2-agonists should never be used as monotherapy to provide asthma control for chronic asthma but should only be combined with anti-inflammatory therapy, particularly ICS, to provide effective therapy for chronic asthma. Moreover, the addition of ICS has not been clearly demonstrated to diminish tolerance to the bronchoprotective effect of LABAs.[7,23,26,28]

Daily use of LABAs and SABAs may actually increase the severity of EIB.[7,23–27] Tolerance may increase with increasing use of SABAs and LABAs, potentially endangering patients with attacks of severe asthma at the time of greatest need for an effective SABA.[7,23–27] The onset of tolerance can be as rapid as 12 to 24 hours after beginning therapy with a SABA or LABA, and recovery may occur within 72 hours of discontinuation of SABA or LABA therapy.[23–27]

Tolerance is often missed because the patient does not require SABAs continuously so that lack of efficacy is not observed by the patient or his or her physician.[23–27] The mechanism of tolerance is postulated to be that, after long-term exposure to SABAs or LABAs, there is uncoupling and internalization or sequestration of β_2-receptors in the mast cells and smooth muscle cells where the receptors are degraded. The net loss of functional β_2-receptors results in downregulation of responsiveness of β_2-agonists, manifesting as reduction in clinical protection to bronchoconstrictive stimuli. Resynthesis of receptors occurs within 72 hours of cessation of exposure to β_2-agonists. Mast cell β_2-receptor downregulation occurs more readily than with smooth muscle so that loss of bronchoprotection precedes loss of bronchodilation.[23–27] Tolerance to bronchoprotection leads to shortening of duration of effect of β_2-agonist, whereas tolerance to bronchodilation is demonstrated by prolongation of time to recovery from bronchoconstriction and by response to usual doses of β_2-agonists.[23–27]

There are no substantial differences in efficacy among the SABAs currently in use.[7,21,22] Two LABAs are currently in use and differ primarily in their onsets of action. Formoterol has an onset of bronchodilation and bronchoprotective action of 5 to 15 minutes compared with salmeterol, which requires 15 to 30 minutes for onset of these actions. Both LABAs may protect for as long as 12 hours after the first dose in patients who have not received a SABA or LABA for at least 72 hours (ie, the drug-naive patient). Unfortunately, even after the first dose of LABA, bronchoprotection for many patients may be for less than 12 hours and the optimal dosing interval for bronchoprotection for EIB may be as short as approximately 6 hours for many patients.[7,21,23,26]

Leukotriene Inhibitors (Summary Statement 42)

The role of LTs in EIB is to sustain the bronchoconstrictive response. Leukotriene inhibitors are effective when used intermittently or daily to provide prophylaxis for asthma and EIB and do not lead to tolerance.[7,11,21–24] Inhibitors of the LT pathway, including LT receptor antagonists (LTRAs) and lipoxygenase inhibitors, are effective as prophylactic agents. Leukotriene receptor antagonists, such as montelukast, have an onset of protection within 2 hours of dosing with duration of activity of 12 to 24 hours.[7,11,21–24] However, the effectiveness of LTRAs is variable among patients, leading to complete inhibition of EIB in some individuals and only partial or no inhibition of EIB in others. Approximately half of patients who receive LTRA are considered responders, with 30% to 80% attenuation of EIB. These percentages may vary, depending on the FEV_1 decrease criteria used to make a diagnosis (eg, $>$10%, $>$15%, or $>$20% decrease in FEV_1) or used to define protection. Patients rarely experience complete

protection. This lack of total protection with the use of LTRAs is expected based on the observation that the pathogenesis of EIB involves additional mediators, including PGs and histamine.[7,11,21–24]

The LTRAs may decrease the time to recovery from EIB when given prophylactically before exercise. However, they are not as effective as β_2-agonists, and unlike β_2-agonists, LTRAs have no ability to reverse airway obstruction when given after obstruction occurs.[7,11,21–24]

Mast Cell Stabilizers (Summary Statement 43)

Cromolyn sodium and nedocromil sodium, when inhaled shortly before exercise, have bronchoprotective action in approximately half of patients to attenuate the severity of EIB, with rapid onset and a short duration of action rarely longer than 2 hours. Neither cromolyn nor nedocromil is currently available in the United States in an inhaled form. Neither agent has any bronchodilator activity. Mast cell stabilizers may be given with another agent to gain added benefits in obtaining bronchoprotective activity. Tolerance to mast cell stabilizers does not develop when the agents are given repeatedly, and these agents have an excellent safety profile.[7,21,22,29,30]

Inhaled Corticosteroids (Summary Statements 44–45)

The occurrence of EIB may be a manifestation of lack of control of chronic asthma so that moderate to severe EIB suggests the need for assessment of therapy or another diagnosis. The National Heart, Lung, and Blood Institute Expert Panel Report 3 lists ICS as first-line therapy for chronic asthma alone or in combination with other agents.[7–9,21,22,28–33] Inhaled corticosteroids have also been shown to have safety and efficacy in decreasing the frequency and severity of EIB in many patients with chronic asthma; ICS are dose and time dependent and may be associated with decreases in inflammatory mediators.[7–9,21,22,28,31,32] Inhaled corticosteroid attenuates BHR to indirect challenge stimuli, including exercise, EVH, mannitol, and AMP and if given for a sufficiently long time, such as months, to direct stimuli such as methacholine. Inhaled corticosteroids have a rapid effect on exhaled nitric oxide (eNO) levels, another manifestation of the effect of ICS on inflammation.[7–9]

Some bronchoprotective effect of ICS has been documented as early as 4 hours after the first dose.[32] After 1 week of long-term use, ICS efficacy begins to plateau[7–9,28,31,32]; however, the bronchoprotection may continue to increase slowly over weeks and even months until it reaches its final plateau.[7–9,21,22,28,31,32] Bronchoprotection with ICS has been demonstrated to occur in 30% to 60% of asthmatic patients with EIB, with marked individual variability ranging from "complete" protection to little or no evidence of protection.[7–9,21,22,28,31,32]

Inhaled corticosteroids do not obviate the need for short-term bronchoprotection for EIB. β_2-agonists can be added, if necessary, for short-term prophylaxis of EIB.[7,21,22] When maintenance ICS are not sufficiently effective to prevent EIB, LTRAs or β_2-agonists can be given to enhance bronchoprotection, if necessary.[7,11,21,22]

Inhaled corticosteroids have not been found to protect against the development of tolerance to β_2-agonist.[21–23,26,31] Nevertheless, the combination of ICS and LABAs in a single inhaler is still recommended for treatment of moderate to severe persistent asthma by National Heart, Lung, and Blood Institute guidelines,[33] even when chronic asthma occurs in a patient who also has EIB. Notably, 1 study in adults[28] indicated better and more complete bronchoprotection and better asthma control when combination ICS-LABA therapy was given compared with use of ICS alone for 4 weeks. A similar study in children indicated a small persistent effect of bronchoprotection when combination ICS-LABA therapy was used compared with ICS alone.[23]

Miscellaneous Therapeutic Agents (Summary Statements 46–47)

Other therapeutic agents have been reported to have efficacy in the prevention of EIB, including approved agents such as anticholinergic agents and theophylline and investigative agents such as antihistamines, inhaled furosemide, ascorbic acid, and inhaled heparin.[7] Further prospective investigations with large populations are needed to confirm the safety, response rate, and degree of efficacy for these investigational agents.[7,34]

Nonpharmacologic Therapy (Summary Statements 48–49)

Nonpharmacologic interventions may be effective in helping to control symptoms of EIB but are generally considered as adjunctive to pharmacotherapy. Preexercise warm-up may be helpful in reducing the severity of EIB for 1 to 3 hours because of the refractory period.[7] Further reduction in EIB may be achieved with postexercise cool-down and breathing through the nose and covering the mouth, particularly in cold, dry weather.[7] Reduction of sodium intake and ingestion of fish oil and ascorbic acid supplementation may be effective in diminishing the severity of EIB as well.[7]

Competitive and Elite Athletes (Summary Statements 50–53)

Exercise-induced bronchoconstriction alone in elite athletes who do not have chronic asthma may have different characteristics than EIB in elite athletes who have chronic asthma or EIB in the general population, including the pathogenesis, presentation, diagnosis, and management of the disorder and the requirement by sport-governing bodies to obtain permission to receive pharmaceutical agents to treat asthma. Airway inflammation in elite athletes may be related to the high intensity of physical training and minute ventilation and inhalation of airborne pollutants by athletes in training or competition environments.[7,35] The diagnosis of EIB in elite athletes may be difficult because history and presentation are not reliable indicators of a diagnosis.[1–3] Objective testing in an elite athlete to diagnose EIB and to secure permission to treat asthma is

mandated by relevant governing bodies of the specific sport in which the athlete is participating.[3]

The management of EIB in athletes who also have chronic asthma is similar in both recreational and elite athletes. However, the management of athletes at any level who only have EIB, unassociated with chronic asthma, is not well understood and requires additional study.[7,35] It is unknown at present whether EIB alone represents a form of overuse syndrome of the lung in elite athletes.[10]

SUMMARY STATEMENTS

Pathophysiology of Exercise-Induced Bronchoconstriction

Definition and Overview

Summary Statement 1. Exercise-induced bronchoconstriction is defined as the transient narrowing of the lower airways that occurs after vigorous exercise. It may appear with or without asthma. The term *EIA* should not be used because exercise does not induce asthma but rather is a trigger of bronchoconstriction. D

Summary Statement 2. Exercise-induced bronchoconstriction occurs in response to heating and humidifying large volumes of air during a short period. The most important determinants of expression of EIB response and severity are the water content of the inspired air and/or the level of ventilation achieved and sustained during exercise. B

Summary Statement 3. Respiratory water loss at high ventilation is associated with airway cooling and dehydration and an increase in osmolarity of the airway surface. B The predominant theory of EIB is the osmotic theory, although the thermal theory may also play a role. C

Summary Statement 4. Exercise itself is not necessary to cause airways to narrow; voluntary hyperpnea of dry air may induce bronchoconstriction similar to exercise. Eucapnic voluntary hyperpnea is used as a surrogate for exercise in the diagnosis of EIB, particularly in athletes. B

Summary Statement 5. People who have EIB without asthma associated with airway inflammation and the presence of eosinophils are likely to be responsive to corticosteroids. B

Summary Statement 6. Exercise-induced bronchoconstriction is accompanied by release of mediators such as PGs, LTs, and histamine. B

Summary Statement 7. In approximately half of patients who have EIB, there is an interval of refractoriness lasting approximately 2 to 3 hours immediately after an episode of EIB during which additional exercise produces little or no bronchoconstriction. B

Genetics and Environment

Summary Statement 8. Gene expression and environmental interaction may be relevant to the EIB phenotype. D

Summary Statement 9. Oxidative stress caused by environmental pollutants that are inhaled during exercise may play an important role in the development and exaggeration of EIB. B

Summary Statement 10. The pathogenesis of EIB in elite athletes may relate to effects on the airways arising from humidifying large volumes of dry air over months of training with or without exposure to environmental irritants, allergens, and viral agents. D

Prevalence

Summary Statement 11. Exercise-induced bronchoconstriction is reported in most asthmatic patients. A

Summary Statement 12. Patients with more severe or less well-controlled asthma are more likely to manifest EIB than patients with less severe or better controlled disease. A

Summary Statement 13. The true prevalence of EIB in the general population is poorly defined because epidemiologic studies of EIB have not differentiated asthmatic vs nonasthmatic populations. In addition, there is no consensus for the end point indicative of a positive response, and the conditions under which exercise is performed frequently differ. B

Summary Statement 14. The prevalence of EIB in elite athletes appears to be higher than in the general population and depends on the type of sport, the maximum exercise level, and environmental conditions. B

Summary Statement 15. The prevalence of EIB varies with history, type of challenge, and conditions under which the challenge is performed. A

Summary Statement 16. The prevalence of EIB with and without asthma may be influenced by age, sex, and ethnicity. C

Diagnosis

Summary Statement 17. Self-reported symptoms alone are not reliable for diagnosis of EIB. B

Summary Statement 18. Optimal EIB management may require confirmation of the diagnosis using objective methods. A

Summary Statement 19. Self-reported symptom-based diagnosis of EIB in the elite athlete lacks sensitivity and specificity and establishes the necessity for standardized, objective challenges using spirometry. B

Summary Statement 20. The indirect challenge (eg, exercise or surrogate such as EVH) is preferred over a direct challenge (eg, methacholine) for assessing EIB in the elite athlete. D

Summary Statement 21. Eucapnic voluntary hyperpnea is the preferred surrogate challenge for the elite athlete participating in competitive sports. D

Summary Statement 22. The intensity of the exercise challenge for the elite athlete should be 95% or greater than actual or estimated HR_{max}, and dry medical-grade air should be used in performing the challenge. D

Summary Statement 23. Hyperosmolar aerosols may also be used as surrogates to exercise. C

Differential Diagnosis

Summary Statement 24. Exercise-induced laryngeal dysfunction, primarily VCD and other glottic abnormalities, may be elicited by exercise and mimic EIB. Inspiratory stridor is

a differentiating hallmark sign with EILD and not with EIB alone. Flattening of the inspiratory curve on spirometric maneuver may be seen concomitant with symptoms. Exercise-induced laryngeal dysfunction may occur alone or with EIB. Failure to respond to asthma management is a key historical feature suggesting EILD. C

Summary Statement 25. Exercise-induced dyspnea and hyperventilation can masquerade as asthma, especially in children and adolescents. C

Summary Statement 26. Shortness of breath with exercise may be associated with underlying conditions due to obstructive lung disease, such as chronic obstructive pulmonary disease (COPD), or restrictive lung physiology, such as obesity, skeletal defects (eg, pectus excavatum), diaphragmatic paralysis, and interstitial fibrosis. B

Summary Statement 27. Shortness of breath accompanied by pruritus and urticaria, with varying other systemic symptoms, suggests EIAna rather than EIB. C

Summary Statement 28. In the absence of objective evidence of EIB, breathlessness with exercise, with or without chest pain, may be caused by cardiovascular, pulmonary, or gastroenterologic mechanisms other than asthma. Appropriate cardiopulmonary testing and/or referral to a cardiologist, pulmonologist, or gastroenterologist may be necessary. B

Summary Statement 29. Exercise-induced dyspnea is seen as a physiologic limitation in otherwise healthy active individuals without bronchospasm. C

Summary Statement 30. The association between EIB and gastroesophageal reflux disease (GERD) is controversial, and probably there is no relationship. A

Summary Statement 31. Psychological factors need to be considered in the differential diagnosis of EIB. D

Summary Statement 32. Dyspnea on exertion, which is prevalent in otherwise healthy, obese individuals, is not associated with EIB. C

Summary Statement 33. Mitochondrial enzyme deficiency with myopathy is a rare cause of exercise limitation. D

Therapy

Introduction

Summary Statement 34. Frequent EIB in asthmatic patients suggests inadequate asthma control and requires patient reevaluation to determine the need for additional therapy. D

Summary Statement 35. Failure of appropriate pharmacotherapeutic agents to prevent EIB indicates the need to reevaluate the diagnosis. D

Summary Statement 36. Several pharmacotherapeutic agents are effective when given for the prevention or attenuation of EIB. They differ in their mechanisms of action and overall effectiveness. In addition, there is both intrapatient and interpatient variability in responsiveness. A

Summary Statement 37. Medications may differ in effectiveness over time because of variability of asthma, environmental conditions, intensity of the exercise stimulus, and tachyphylaxis. A

β_2-Adrenergic Receptor Agonists

Summary Statement 38. Inhaled β_2-adrenergic receptor agonists are the most effective group of agents for short-term protection against EIB and for accelerating recovery of FEV_1 to baseline when given after a decrease in FEV_1 after exercise. A

Summary Statement 39. When given as a single dose or on an intermittent basis, SABAs and LABAs may protect against or attenuate EIB; SABAs are usually effective for 2 to 4 hours and LABAs for up to 12 hours. A

Summary Statement 40. Daily use of β_2-adrenergic agents alone or in combination with ICS usually will lead to tolerance manifested as a reduction in duration and/or magnitude of protection against EIB and a prolongation of recovery in response to SABA after exercise. Therefore, monotherapy with adrenergic agents is generally recommended for use only on an intermittent basis for prevention of EIB. A

Summary Statement 41. Regular (ie, daily) use of β_2-agonists for EIB leads to relative loss of efficacy of the agent. A

Leukotriene Inhibitors

Summary Statement 42. Daily therapy with LT inhibitors does not lead to tolerance and can be used for intermittent or maintenance prophylaxis; however, it provides protection that may not be complete and has no use to reverse airway obstruction when it occurs. A

Mast Cell Stabilizers

Summary Statement 43. Cromolyn sodium and nedocromil sodium (currently not available in the United States in an inhaled form) when inhaled shortly before exercise attenuate EIB but have a short duration of action. They do not have a bronchodilator activity. They may be effective alone or as added therapy with other drugs for EIB. A

Inhaled Corticosteroids

Summary Statement 44. Although ICS therapy can decrease the frequency and severity of EIB, its use does not necessarily eliminate the need for additional acute therapy with β_2-adrenergic agonists or other agents. A

Summary Statement 45. Inhaled corticosteroid therapy does not prevent the occurrence of tolerance from daily β_2-agonist use. A

Anticholinergic Agents

Summary Statement 46. Although ipratropium bromide has been inconsistent in attenuating EIB, a few patients may be responsive to this agent. A

Methylxanthines, Antihistamines, and Other Agents

Summary Statement 47. Drugs in several other pharmacotherapeutic classes, including theophylline, antihistamines, calcium channel blockers, -adrenergic receptor antagonists, inhaled furosemide, heparin, and hyaluronic acid, have been examined for actions against EIB with inconsistent results. B

Nonpharmacologic Therapy

Summary Statement 48. Preexercise warm-up may be helpful in reducing the severity of EIB. A

Summary Statement 49. Reduction of sodium intake and ingestion of fish oil and ascorbic acid supplementation may be helpful in reducing the severity of EIB. A

Competitive and Elite Athletes

Summary Statement 50. Exercise-induced bronchoconstriction alone in elite athletes may have different characteristics than EIB with asthma in elite athletes or EIB in the general population. These divergent characteristics may include pathogenesis, presentation, diagnosis, management, and the requirement by governing bodies to obtain permission to receive pharmaceutical agents. D

Summary Statement 51. Airway inflammation in elite athletes may be related to the high intensity of physical training, high minute ventilation, and inhalation of airborne pollutants and allergens. D

Summary Statement 52. The diagnosis of EIB, whether alone or with asthma, in elite athletes may be difficult because history and presentation are not reliable. Objective testing is necessary to diagnose the condition accurately. A

Summary Statement 53. In general, the treatment of EIB in patients who have asthma is similar in both recreational and elite athletes. However, the efficacy of therapy for EIB alone in athletes at any level is not well established. A

Pathophysiology of Exercise-Induced Bronchoconstriction

Definition and Overview

Summary Statement 1. Exercise-induced bronchoconstriction is defined as the transient narrowing of the lower airways that occurs after vigorous exercise. It may appear with or without asthma. The term *EIA* should not be used because exercise does not induce asthma but rather is a trigger of bronchoconstriction. D

Exercise-induced bronchoconstriction is usually measured as a reduction in FEV_1 after exercise and defined as a decrease of 10% to 15% of the preexercise value.[1–6,36–40] Exercise-induced bronchoconstriction is a manifestation of BHR and is often the first sign of asthma. A β_2-agonist, by inhalation, is the most widely used treatment given immediately before exercise to prevent EIB. In clinically recognized asthmatic patients, EIB is associated with airway inflammation, and decrement of EIB will occur in most cases within 12 weeks of daily treatment with ICS alone.[9,28,41,42]

Summary Statement 2. Exercise-induced bronchoconstriction occurs in response to heating and humidifying large volumes of air during a short period. The most important determinants of expression of EIB response and severity are the water content of the inspired air and/or the level of ventilation achieved and sustained during exercise. B

At resting ventilation under most inspired air conditions, the air is usually fully conditioned by the time it has passed over the nasal mucosa. During exercise, there is a switch from nasal to mouth breathing as ventilation increases to 30 L/min or more.[43] The number of generations of the lower airways required to complete the conditioning of the air depends on the following: ventilation rate, water content and temperature of the inspired air, temperature of the airway wall, and availability of airway surface liquid (ASL) to provide humidification.[44] The cumulative surface area of the airways and the ASL volume are sufficiently large that it is unlikely that unconditioned air will enter the alveoli. In contrast, the cumulative surface area and the volume of the ASL in the first 10 generations are surprisingly small—at approximately 190 cm^2 with less than 1 mL in volume of ASL—compared with the cumulative surface area to generation 17 (3,100 cm^2).[45]

The most important determinants of EIB severity are the water content of the inspired air and the level of ventilation achieved and sustained during exercise. The dryer the inspired air and the higher the ventilation during the 6 to 8 minutes of exercise, the greater the likelihood of a positive response to exercise in a susceptible person.[46–49]

Direct measurements of airway temperature have shown that inspired air at 22°C and 9 mg H_2O at 60 L/min is not fully conditioned at the fifth airway generation.[50] Mathematical models have demonstrated that under these conditions the air is fully conditioned by the 12th airway generation. Airways of generation 12 have a diameter about 1 mm.[51] Full conditioning of inspired air of subfreezing temperature involves more than 12 generations, and these very small airways that have a diameter less than 1 mm are susceptible to injury from the cold air.

When air fully saturated with water is inspired at body temperature during exercise, EIB is markedly inhibited or even completely prevented.[48,52,53] Any intervention that reduces respiratory water loss reduces severity of EIB, such as reducing the intensity and duration of exercise,[17,54] reducing the ventilation by aerobic conditioning,[55] increasing water content of the inspired air, and breathing via the nose or using a face mask.[56–58] All of these interventions are consistent with the observation that the greater the number of generations of airways recruited to condition the air, the more likely EIB will occur and the more severe it will be for a given individual. The involvement of peripheral airways in the conditioning process is probably important because the density of mast cells is the greatest in the periphery.[12,51,59–61]

Summary Statement 3. Respiratory water loss at high ventilation is associated with airway cooling and dehydration and an increase in osmolarity of the airway surface. B The predominant theory of EIB is the osmotic theory, although the thermal theory may also play a role. C

Respiratory water loss at high ventilation is associated with cooling of the airways[50] and dehydration of the ASL volume with subsequent increase in osmolarity.[62] Cooling and hyperosmolarity probably act independently as stimuli for the airways to narrow. Cooling is a mechanical stimulus that involves reactive hyperemia of the bronchial vasculature,[63,64]

whereas hyperosmolarity induces mediator release and subsequent contraction of the BSM.[12,13]

When air of subfreezing temperature is inspired during exercise, airway cooling causes vasoconstriction of the bronchial vasculature.[65] On cessation of exercise, when ventilation falls and the airways rewarm, a reactive hyperemia with vascular engorgement and edema of the airway wall occurs.[66] This is known as the thermal theory of EIB. The proponents of this theory consider that the vascular events explain all the airway narrowing seen with EIB.[63,64] The thermal theory of EIB does not include BSM contraction or mediator release in the mechanism of EIB.[63,64]

The osmotic theory of EIB developed when it was demonstrated that abnormal cooling of the airways was not a prerequisite for EIB and that the airways of asthmatics were sensitive to small changes in osmolarity.[62,67–81] The osmotic theory has been supported by observations that mast cells and eosinophils release mediators in response to an increase in osmolarity.[82–84]

Dehydration of the ASL causes an increase in its ion content and osmolarity when water on the airway surface is evaporated faster than it is returned by condensation or from the epithelial cell or submucosa.[51,85] Dehydration of the ASL has been demonstrated by a marked reduction in mucociliary clearance during dry air breathing both in asthmatic and healthy patients.[86]

The cooling and osmotic theories of EIB may operate together under conditions of breathing cold dry air when the vascular effects may amplify the contractile effect of the mediators.[12,13] As the temperature of the inspired air increases toward body temperature, the osmotic effects of water loss will become more important than cooling. Airway cooling does not play a significant role in the EIB that occurs with breathing hot dry air.[69–71,87,88]

Summary Statement 4. Exercise itself is not necessary to cause airways to narrow; voluntary hyperpnea of dry air may induce bronchoconstriction similar to exercise. Eucapnic voluntary hyperpnea is used as a surrogate for exercise in the diagnosis of EIB, particularly in athletes. B

Exercise itself is not necessary to cause airways to narrow; voluntary hyperpnea of dry air may induce bronchoconstriction similar to exercise.[49,89–92] Thus, EVH of dry air containing 4.9% to 5% carbon dioxide is often used as a surrogate for exercise in the diagnosis of EIB, particularly in athletes.[93–96] The EVH test for EIB was standardized many years ago to evaluate military recruits for EIB.[92,97,98] Eucapnic voluntary hyperpnea is recommended by the European Respiratory Society/European Academy of Allergy and Clinical Immunology Task Force[99] to identify EIB in athletes and is included in the World Anti-Doping Agency assessment of asthma (www.wada-ama.org/Documents/Science_Medicine/). Eucapnic voluntary hyperpnea should not be performed on a patient who has an FEV_1 below 70% of predicted and only with caution if FEV_1 is below 80% of predicted because of the risk of a serious decrease in FEV_1.

Summary Statement 5. People who have EIB without asthma associated with airway inflammation and the presence of eosinophils are likely to be responsive to corticosteroids. B

In people with clinically recognized asthma, EIB is related to the presence of eosinophils; those with EIB tend to have a greater concentration of eosinophils in sputum relative to those without EIB.[100] Sputum eosinophils have also been reported to increase acutely in response to exercise,[101] although this has not been a universal finding.[102] There is an association between the percentage of eosinophils in sputum and the severity of EIB.[103] An association between peripheral blood eosinophil counts and severity of EIB has also been reported.[104] As expected, the reduction in EIB severity after treatment with ICS is also accompanied by a reduction in percentage of eosinophils in sputum.[8,9,28,32,41,42,103,105,106]

Summary Statement 6. Exercise-induced bronchoconstriction is accompanied by release of mediators such as PGs, LTs, and histamine. B

There is both indirect and direct evidence for mediators being important in EIB. Some studies show the benefit of specific pharmacologic antagonists and mast cell–stabilizing agents on EIB, and other studies show increases in mediator concentrations in sputum and urine after exercise.

Mast cells have long been thought to be an important source of mediators for EIB because drugs that prevent mast cell release of mediators or antagonize the effects of these mediators reduce the severity of EIB.[79,80,107–118] Prostaglandin 2 (PGD_2), is the major mast cell specific mediator in EIB. Mast cells also generate LTs and histamine.[83,119] In addition to mast cells, eosinophils are also a potential source of LTs.[84] These same mediators, beyond acting on BSM to cause contraction and the airways to narrow, can also increase microvascular permeability (MVP), leading to edema.[120]

The increased urinary excretion of LTE_4 and the stable urinary metabolite of PGD_2, $9\alpha,11\beta PGF_2$ have provided evidence that arachidonic acid metabolites are probably involved in EIB.[11,30,32,80,116,117] Although early studies found only small increases in histamine in arterial plasma in response to exercise,[121,122] recent studies of sputum have confirmed that EIB is associated with release of histamine.[116,117]

Importantly, inhibition of the release of these mediators is associated with reduction in severity of EIB.[32] Sodium cromoglycate and the related compound nedocromil sodium inhibit EIB by stabilizing mast cells.[79,80,109,111,114,115] This has been demonstrated by the finding that PGD_2 is released in response to the osmotic stimulus mannitol.[30,123]

Leukotriene antagonists modify the maximum decrease in FEV_1 and the time of recovery after EIB.[112,124] Histamine antagonists have been observed to have variable activity on EIB with few investigators reporting complete inhibition of EIB in most patients.[107,110,113] It is of interest that histamine antagonists may be more effective in preventing EIB in those exercising strenuously.[125] With strenuous exercise, the more peripheral airways are likely to be involved in conditioning the air and histamine release from mast cells is more likely to occur.[61,125]

Many mediators increase MVP,[120] an event that is thought to play a role in EIB. An increase in MVP is usually identified by a change in markers of microvascular leakage. Thus, an increase in MVP after exercise has been demonstrated by a change in sputum-serum ratio of albumin.[126] The increase in this ratio has been shown to relate to severity of EIB. Furthermore, vascular endothelial growth factor and angiopoietin 2 also stimulate MVP, and levels of these substances measured after exercise are also related to severity of EIB.[126–128] The potential role for increased MVP in the pathophysiology of EIB is clear in that it could act to amplify the airway narrowing caused by BSM contraction. However, MVP may also play a role in the pathogenesis of EIB in relation to airway injury (see below).

Summary Statement 7. In approximately half of patients who have EIB, there is an interval of refractoriness lasting approximately 2 to 3 hours immediately after an episode of EIB during which additional exercise produces little or no bronchoconstriction. B

In approximately half of patients who have EIB after the initial episode of EIB, there is an interval of refractoriness lasting approximately 1 to 3 hours during which additional exercise produces little or no bronchoconstriction.[129–131] The precise mechanism for this refractory period is not fully understood; however, recent findings suggest that the refractory period could be explained by BSM becoming tolerant to the effect of mediators.[132] The refractory period may be prevented by taking nonsteroidal anti-inflammatory drugs for 3 days. Nonsteroidal anti-inflammatory drugs inhibit the cyclooxygenase pathway and thus production of several PGs. Some investigators propose that PGE_2, an endogenous mediator that causes smooth muscle relaxation, may play a role in the development of refractoriness.[133–136]

Genetics and Environment

Summary Statement 8. Gene expression and environmental interaction may be relevant to the EIB phenotype. D

The few studies that have investigated gene expression linked to EIB have used only asthmatic patients who express the EIB phenotype. Some studies have identified increased expression of genes involved in eicosanoid release in patients who have asthma, whereas others found no relationship.[15,137] The polymorphism IL-13^{+}2044G/A has been strongly associated with atopy and severity of EIB in Korean children, whereas the IL-13^{-}1112C/T and the haplotype of IL-13 polymorphisms were associated with LTRA responsiveness.[138]

One group of researchers[16] demonstrated increased expression of mucin 5AC (MUC5AC) after an exercise challenge that was associated with the severity of EIB. Mucins such as MUC5AC may significantly contribute to airflow obstruction.[139] Moreover, associations were found between levels of MUC5AC and cys-LTs and neurokinin A in the airways and suggested a mechanism whereby MUC5AC is released by cys-LT activation of sensory airway nerves.[16] Using phenotypically distinct asthmatic patients, those without and with EIB, the same authors[140] identified different patterns of gene expression. In particular, after exercise challenge, expression of transglutaminase 2 was increased. Transglutaminase 2 was further shown to augment enzymatic activity of phospholipase A_2 group X ($sPLA_2$-X), an enzyme that catalyzes eicosanoid (cysteinyl-LTs) formation. High $sPLA_2$-X has been identified in asthmatic patients and has been shown to increase further after exercise challenge in asthmatic EIB phenotypes.[141]

Summary Statement 9. Oxidative stress caused by environmental pollutants that are inhaled during exercise may play an important role in the development and exaggeration of EIB. B

Oxidative stress is an important feature in the pathogenesis of asthma[142] and may enhance EIB-related mediator production.[143] Oxidative stress probably results from both an increase in reactive oxygen/nitrogen species and depletion of antioxidants in the airways. Inhalation of high particulate matter (PM) air during exercise has been shown to reduce alveolar contribution to eNO, decrease total nitrate, and increase lipid peroxidation in exhaled breath condensate and was related to postexposure decrease in FEV_1.[144] Increased concentration of 8-isoprostane, a marker of airway oxidative stress, in exhaled breath condensate is associated with EIB.[143]

Ozone is a major oxidant generated from a photochemical reaction of hydrocarbons and nitrogen oxides from combustion emissions that has been shown to trigger EIB.[145,146] Exposure studies show decrements in FEV_1 ranging from 0% to 48% with mild ozone exposure.[147,148] Glutathione S-transferases are found in high concentrations in the lung and are involved in antioxidant defense pathways[149] and glutathione homeostasis.[150] A single nucleotide polymorphism of glutathione S-transferase π ile105 has recently been implicated in the development of new onset asthma and EIB in children who participate in team sports in high ambient ozone, with a hazard ratio for new-onset asthma of 6.15 (range, 2.2–7.4).[151]

Airborne PM generated from combustion emissions is associated with the formation of reactive oxygen species that influence mediator release from airway cells.[152,153] Exposure to high levels of PM is associated with increased emergency department visits,[154,155] increased bronchodilator use,[156] and bronchoconstriction after exercise in asthmatic and nonasthmatic individuals.[157] High levels of airborne PM have been identified at indoor ice rinks that use a fossil-fueled (gas, propane, or natural gas) ice resurfacer[158–160] and at athletic fields that are close to high automobile and truck traffic.[161] The ice rink air exposure during exercise coupled with a genetic susceptibility could account for the observed high prevalence of asthma and EIB in athletes exercising in an ice rink.[159,160,162–165] Cysteinyl-LTs appear to be important mediators in PM-induced bronchoconstriction; 1 study[166] found increased protection against EIB in a high pollution environment by the LTRA montelukast. Diesel exhaust particles have been shown to enhance the induction of allergy and to increase inflammatory cytokines and cysteinyl-LTs in animal models.[167] Likewise, secondhand tobacco smoke has been shown to increase cysteinyl-LT–related albuterol usage

and montelukast responsiveness in children exposed to tobacco smoke.[168]

Summary Statement 10. The pathogenesis of EIB in elite athletes may relate to effects on the airways arising from humidifying large volumes of dry air over months of training with or without exposure to environmental irritants, allergens, and viral agents. D

Exercise-induced bronchoconstriction is commonly seen in highly competitive athletes, especially in those competing at the national and international level.[1,2,95,164,169–171] The reason that this condition is seen in such well-trained athletes is not fully understood, but airway injury and the environment may play an important role, particularly in athletes reporting onset of asthma at older than 22 years of age.[10,35]

Injury of the airways may arise from conditioning large volumes of dry air over months of training, with or without exposure to environmental irritants, allergens, and viral agents.[158,159,171–178] Repair follows injury and the process is associated with microvascular leakage. It is possible that BHR to inflammatory mediators and pharmacologic agonists may develop as a result of repeated exposure to plasma-derived products that cause a change in the contractile properties of BSM.[10,126,179–183]

A hypothesis has now been postulated relating pathogenesis of BHR and EIB to airway injury in athletes. This hypothesis is based on observations reported by many investigators[10] that recruitment of the very small airways (<1 mm) in the air conditioning process may be accompanied by injury of the epithelium. Such injury would be associated with plasma exudation, and in the process of repetitive injury and exudation, the contractile properties of the BSM would be altered, rendering it more sensitive. One potential outcome may be BHR to methacholine as demonstrated in winter athletes.[178,184–186] It is important to know whether methacholine responsiveness in athletes is a manifestation related to airway injury rather than a sign of "classic" asthma. The notion that BHR may be related to injury is supported by the return to normal responsiveness when athletes are out of season[187] or after retirement.[188] For summer athletes who are more likely to be atopic and have higher IgE levels, the hypothesis proposes that "passive" sensitization of the BSM can occur in vivo during the injury/exudation process. In this case, the BSM may become more responsive to contractile mediators such as LTE_4 released into the circulation in response to intense exercise.[189] This may explain why some athletes can benefit from use of LT antagonists and other agents that prevent release of mediators or antagonize their action.[166]

One of the important concepts in this hypothesis is the presence of mast cells in the small airways of healthy people and their proximity to the BSM in these airways.[61] The presence of mast cells adjacent to the smooth muscle or a mast cell myositis is a relatively new concept in defining asthma.[60,190] As noted above, mast cell mediators released in the periphery provoke smooth muscle contraction and airway inflammation, which are the hallmarks of asthma.

The potential for β_2-agonists to inhibit or enhance development of BHR and EIB also needs to be considered. There are well-known beneficial effects of β_2-agonists: these include relaxation of BSM, stabilization of mast cells, and stimulation of Cl^- ion secretion and water to the airway surface. It is possible that given in the short term, β_2-agonists reduce airway injury and microvascular leakage.[191] By contrast, the same drugs given in the long term may cause mast cells to become more sensitive or unstable to stimuli because β_2-receptors are downregulated with long-term use.[192,193] The sensitivity of the smooth muscle may be increased because of an increase in number of histamine receptors[194] or cross talk between the relaxing and contractile pathways through the Gs protein.[195]

There are other mechanisms whereby elite athletes could develop BHR. One is respiratory tract infection. There is a higher frequency of infections in athletes compared with controls. The reason is thought to be due to the suppressed immunity that occurs between 3 and 72 hours after exercise, known as the "open window" theory.[177] The role of viruses in changing reactivity may relate to effects on the β_2-receptor. Bronchial hyperresponsiveness to histamine is prolonged when training was continued during an upper respiratory tract infection.[196] A low serum IgA secretion rate during a marathon was shown to be the best predictor of infection.[197] The finding of lymphoid aggregates in cross-country skiers[198] may indicate an immune response to infection.[199,200]

The difference in the pathogenesis of EIB and BHR may be the reason there are differences in response to treatment between athletes and patients with classic asthma.[201,202] For example, neutrophils rather than eosinophils may be more common in those with exercise-induced airway injury, making the problem less amenable to treatment with inhaled steroids.[201] By contrast, macrolides may have potential for modifying the inflammation of neutrophils.[203]

Forty years ago, EIB was thought to involve the release of mast cell mediators[7] because sodium cromoglycate, a mast cell–stabilizing agent with no action on BSM, was effective in inhibiting EIB. The recognition that the rate of water loss from the airway surface was the determining factor for EIB severity led to the thermal (airway cooling) and osmotic (airway dehydration) hypotheses of EIB. After the introduction of ICS, it became clear that the pathophysiology of EIB also involved inflammation of the airways. During the last 10 to 15 years, the techniques used to measure mediators have become much more sensitive, allowing PGs, LTs, and histamine to be identified in sputum and urine after exercise. Observations that these mediators are indeed present confirm the role of the mast cell and other inflammatory cells in EIB. The increasing recognition that EIB can occur in healthy people (eg, elite athletes, military recruits, and schoolchildren) without classic signs and symptoms of asthma has led to airway injury being suggested as important in the pathogenesis of EIB. Conditioning vast volumes of dry air has the potential to injure the peripheral airways in athletes, as does

Table 1. Prevalence of EIB in Different Populations

Population	Challenge test	Sport	Prevalence of EIB, %	Reference
Adults	EVH	Fitness	19	212
High school athletes	EVH	Not stated	38	213
Adolescents	Exercise	High school	28	214
College athletes	EVH	Various athletes	35–36	2
Children from India	Exercise	Urban/rural	13/10	215
Adolescents	Exercise	Various sports	9.4	216
Olympics	Exercise	Winter sports	18–50	164
Elite	Field exercise/methacholine	Skiers	37.5/8.3	178
Elite	Exercise	Figure skaters	35	162
Elite	Exercise	Figure skaters	30	163
Elite	EVH	Summer athletes	50	4
Olympics	EVH/exercise	Winter sports	45/29	94

Abbreviations: EIB, exercise-induced bronchoconstriction; EVH, eucapnic voluntary hyperpnea.

the environment, which is increasingly being considered as important in the pathogenesis of EIB.

Prevalence

Exercise-induced bronchoconstriction is reported in most asthmatic patients but also occurs in the absence of chronic asthma. Exercise-induced bronchoconstriction is very common in athletes. The prevalence of EIB is significantly influenced by the criteria used for diagnosis. The use of self-reported symptoms to make the diagnosis of EIB will likely misdiagnose asthma in patients who do not have EIB and miss people who have the condition.[1,204–206] Self-reported symptoms should not be relied on solely for the diagnosis of EIB without the concomitant use of spirometry and bronchial provocation challenge, including reversibility after β_2-agonist, to confirm the diagnosis.

The prevalence of EIB is also influenced by age, sex, ethnicity, and the environmental conditions (eg, air temperature and humidity, allergen content, and pollution) in which exercise is performed. This largely affects the prevalence of EIB in different population samples (Table 1).

Summary Statement 11. Exercise-induced bronchoconstriction is reported in most asthmatic patients. A

Summary Statement 12. Patients with more severe or less well-controlled asthma are more likely to manifest EIB than patients with less severe or better controlled disease. A

Summary Statement 13. The true prevalence of EIB in the general population is poorly defined because epidemiologic studies of EIB have not differentiated asthmatic vs nonasthmatic populations. In addition, there is no consensus for the end point indicative of a positive response, and the conditions under which exercise is performed frequently differ. B

The occurrence of bronchoconstriction, especially with symptoms during or after exercise, is one of the common characteristics of asthma, but it also occurs in the absence of asthma. In asthmatic patients, EIB in itself is a marker of poor control and suggests the need to initiate or step up therapy.[33,207] The reported prevalence of EIB varies considerably, depending on the severity and control of asthma in the patients being evaluated.

Exercise-induced bronchoconstriction is a common disorder in children.[208,209] The few data available from cross-sectional studies performed over time seem to indicate that the prevalence of EIB is increasing, in parallel with the increasing prevalence of asthma. A survey in 1973[210] and again in 1988[211] examined 12-year-old children in South Wales who had a decrease of 15% in peak expiratory flow rate after a free run for 6 minutes. On the basis of this measure, they found an increase in prevalence of EIB from 6.7% to 7.7%. The lower prevalence of EIB observed in 2003 (4.7%) may be confounded by the increased number of children taking ICS. Accordingly, the data from these studies showed that the percentage of children who had asthma in the last 12 months was 4.2%, 9.1%, and 15.4% and the percentages who ever had asthma was 5.5%, 12.0%, and 27.3% in 1973, 1988, and 2003, respectively. Otherwise, there is a paucity of data from cohort studies in children examining changes in prevalence of EIB over time and virtually no data in adults. Table 1 indicates that prevalence varies widely, depending on the factors that are being studied and controlled, such as level of intensity of exercise, population under study, and environmental condition.

A study using EVH[212] reported a presumed prevalence of EIB of 19.4% in 212 adults without a history of asthma. In 2007, another researcher[217,218] reported that individuals with a family history of asthma may have a higher prevalence of EIB after running than those who do not have a positive family history. Exercise-induced bronchoconstriction is also more frequent in atopic individuals,[171,219] including those with allergic rhinitis,[220] and after respiratory viral infections and other respiratory diseases.[221] It is unclear what the relationship is between the natural history of EIB when not associated with asthma and the subsequent development of asthma.

Summary Statement 14. The prevalence of EIB in elite athletes appears to be higher than in the general population

and depends on the type of sport, the maximum exercise level, and environmental conditions. B

The need for objective data to diagnose EIB is especially important in the elite athlete because of the establishment of definitive criteria that must be met to allow the use of β_2-agonists in or out of competition.[35] No test for EIB is fully sensitive or specific, and thus, no test is sufficient to substantiate or exclude the diagnosis of EIB in all athletes. Additional variability, such as the passage of time and different environments, may affect the ability to detect BHR.

Reports of the occurrence of asthma symptoms in elite athletes have varied from none to 61%,[222,223] depending on the sport and environment.[1,158,160,162,164,174,222,224–228] In fact, higher prevalence rates are reported in certain populations, such as in elite endurance athletes, and in unique environments, such as competitive skaters and cross-country skiers.[35,165,228] Some investigators[222,223] suggested that endurance athletes, whether summer or winter, had considerably more symptoms than athletes participating in less aerobic sports. Overall, this study suggested that based on symptoms as many as 1 in 4 athletes had EIB. Using a questionnaire in recreational athletes, a similar prevalence of asthma symptoms was reported.[229] However, these data do not suggest that the individuals who report asthma are the same as those who have a positive exercise challenge. However, a similar prevalence of EIB in winter Olympic athletes has been reported based on objective data using an exercise challenge.[164] Certain populations have a higher than expected prevalence based on unique circumstances, such as the high prevalence of EIB in skaters (20%–35%) that has been attributed to high emission pollution from ice cleaning equipment and cold dry air.[158,159] A similar example is the extremes of cold dry air, such as that to which cross-country skiers are exposed, which may increase the prevalence of EIB to 30% to 50%.[230] Similarly, another study[170] found as many as 78% of elite cross-country skiers have symptoms and/or hyperresponsive airways.

Athletes participating in the 1996 summer sports also have variations in EIB prevalence, which may depend on the sport in which they participate. For example, long distance runners may have a prevalence of 17%, whereas speed runners may have a prevalence of 8%.[174] Whether these differences are significant may depend on how the test was performed rather than on a difference in the sports for athletes who expend a similar amount of work. By survey, none of the US Olympic divers and weightlifters had symptoms, whereas 45% of mountain bikers experienced symptoms, consistent with the hypothesis that endurance sports have a higher prevalence of associated EIB during sport participation.[222]

Table 2. Percentage of Athletes Participating in the Olympic Summer Games Notifying or Making Application to Use IBAs

Games	Total No. of Athletes	No. (%) Applying to Use IBAs
Atlanta (notified)	10,677	383 (3.6)
Sydney (notified)	10,649	607 (5.7)
Athens (approved)	10,653	445 (4.2)
Beijing (approved)	10,810	781 (7.2)

Abbreviation: IBAs, inhaler β_2-agonists.

Table 3. Athletes Notifying or Making Application to Use IBAs in 3 Sequential Olympic Summer Games Based on Type of Sport

Sport	No. (%) Applying to Use IBAs		
	Sydney (2000)	Athens (2004)	Beijing (2008)
Triathlon	24 (24.0)	10 (10.1)	28 (25.7)
Cycling	81 (17.0)	63 (13.5)	87 (17.3)
Modern pentathlon	7 (14.6)	8 (12.5)	9 (19.1)
Swimming	163 (11.2)	121 (8.4)	202 (19.3)
Rowing	48 (8.8)	34 (6.1)	70 (12.8)
Canoeing	23 (7.0)	16 (4.9)	9 (2.8)
Athletics (track and field)	87 (4.1)	87 (4.4)	117 (5.8)
Field hockey	15 (4.3)	12 (3.1)	41 (10.7)

Abbreviation: IBAs, inhaler β_2-agonists.

Poor air quality may also be associated with a high prevalence of EIB.[231] In swimmers, chloramines above the water may trigger EIB. Interestingly, swimmers with longer duration of exposure tend to have a higher prevalence of EIB.[232] Discontinuation of swimming resulted in a decreased incidence of EIB.[188] As noted above, the high prevalence of EIB in skaters (20%–35%) has been attributed to high emission pollution from ice cleaning equipment and cold dry air.[158,159] Seasonal variation of EIB is also described in Olympic athletes.[171] For example, when using a 6.5% decrease in FEV_1 with running, 28% of runners had probable EIB. Of these runners, 22% had EIB that occurred only in the winter and 7% had EIB only during the pollen season.[171] Seasonal difference was also demonstrated by another investigation,[233] which found that 35% of runners training in the cold reported an increased prevalence of EIB compared with summer when the prevalence was less.

Data collected from the summer Olympics between the years 1992 and 2008 have documented an increasing percentage of elite athletes reporting asthma. This trend follows a similar increase noted in the general population. Confounders, such as the requirement of the Olympic Committee to have an objective diagnosis of EIB to permit utilization of albuterol, may account for the large increase of percentages between 2004 and 2008. Similarly, the difference in reporting requirements over the years makes the data difficult to interpret. Table 2 contains the data on asthma reporting in the Summer Games. Table 3 contains data demonstrating the influence that particular sports have on the reporting of asthma from athletes. Again, the data may be biased by differences in reporting requirements for each of the Games.

Summary Statement 15. The prevalence of EIB varies with history, type of challenge, and conditions under which the challenge is performed. A

By examining responses to history questions on their intake forms required by the US Olympic Committee athletes participating in the 1996 Summer Olympic Games, investi-

gators[222] found 0% to 45% of summer athletes, depending on sport, answered questions compatible with having EIB. The prevalence varied significantly among different sports, with nonendurance sports having minimal levels while endurance sports had higher prevalences. By using the same data extraction method, the same researcher[223] found that up to 60.7% of athletes participating in Nordic skiing events responded to questions that suggested they had EIB.

A limitation of determining prevalence by survey is evident by work performed by investigators,[1] who found that those who had symptoms did not necessarily have a positive challenge result and those who had a positive challenge result did not necessarily have symptoms. Other researchers[234] demonstrated this in adolescent athletes with and without a history suggesting EIB. Those with a history of abnormal baseline spirometry suggesting a risk for EIB had a positive exercise challenge (at least a 15% decrease in FEV_1) in 8 of 48 tested (17%), whereas in those students who had no risk factors, 14 of 118 (12%) had a positive challenge result. Thus, symptoms suggest a positive challenge result, but most of those who had positive challenge results were not at risk. This suggests that patients with a history of chronic asthma are more likely to have positive exercise challenges, but individuals without a history of asthma will also have a positive challenge result.

Another study[4] used different techniques in an attempt to clarify prevalence of EIB. These investigators challenged 50 elite athletes with and without a history of asthma documented by questionnaire with methacholine provocation and with EVH. The results showed that of the 42 athletes who reported respiratory symptoms, 9 had a positive methacholine test result and 25 had a positive EVH test result. Methacholine had an excellent negative predictive value, but only a 36% sensitivity for identifying those with a positive EVH test result.

These findings are consistent with the observations found in 2 more studies,[227,235] which demonstrated that EIB and asthma symptoms do not correlate well with eNO, results of bronchial lavage, or challenges with AMP or histamine challenge. Data from this group confirmed that typical signs and symptoms consistent with asthma are not always found in athletes who have EIB. Conversely, some athletes thought to have EIB probably do not. It has been demonstrated that symptoms are neither sensitive nor specific to suggest a positive EVH test result as evidence for EIB.[2] This testing found that 36% of college athletes without symptoms had a comparable decrease of 10% in FEV_1 and a similar number (35%) of those with symptoms had such a decrease with EVH. Other investigators[236] challenged 33 elite swimmers with EVH challenge, 8-minute swim challenge, and 8-minute laboratory cycle challenge. A 10% decrease in FEV_1 was considered positive; 55%, 3%, and 12% were considered positive by EVH, swim test, and cycle test, respectively.

Summary Statement 16. The prevalence of EIB with and without asthma may be influenced by age, sex, and ethnicity. C

Researchers[237] exercised 15,241 children using a 6-minute run and a decrease of 15% for peak flow as an indicator of EIB. In this cohort, girls (8.5%) were more likely than boys (6.4%) and those from urban settings (8.9%) were more likely than those from rural environs (7%) to have a positive challenge result. As expected in all populations, symptoms were a poor predictor of positive challenge results.

The frequency and severity of asthma may vary by sex, with males having greater frequency during childhood but females having more severe asthma during adulthood.[238,239] In contrast to the above findings,[237] another study[240] failed to demonstrate sex differences in EIB. However, these investigators found that with increasing age, the frequency of EIB decreased. Frequency of asthma and EIB may also vary by sex in elite athletes. In winter sports, females appear to exceed males in prevalence of EIB. In US Olympic winter sports, the prevalence of EIB by exercise challenge test was 26% in female and 18% in male athletes with a combined percentage of 23%.[164] Using questionnaires and methacholine challenges, investigators[241] found that the prevalence of exercise-associated asthma symptoms and BHR was higher in female than male athletes. When using EVH as a surrogate challenge for EIB, another study[2] failed to find such a difference in prevalence between the sexes.

Urbanization has been shown to be associated with an increase in prevalence of asthma and EIB. Using a free run and peak flow testing for EIB, rural children, urban poor, and wealthy urbanites had a prevalence of 0.1%, 3.1%, and 5.8%, respectively.[242]

A standardized free running test with peak flow monitoring demonstrated that African Americans had a higher prevalence of EIB than European Americans (13% and 2%, respectively).[243] When assessing 9-year-old children with cycle ergometry in Great Britain, ethnicity differences in EIB were also evident, with Asian children (originating from the Indian subcontinent) having a prevalence of 3.6 times higher than that of white, inner-city children.[244]

In summary, EIB prevalence is affected by age, sex, ethnicity, and urbanization. Elite athletes may have a high prevalence of EIB, which can be associated with extreme atmospheric conditions, such as high levels of pollen, pollution, cold air, and chemicals, particularly in the training environment. Exercise-induced bronchoconstriction can be demonstrated in people without symptoms, but symptoms are not a sensitive predictor of EIB. Prevalence of EIB varies by the test used to detect it.

Diagnosis

Summary Statement 17. Self-reported symptoms alone are not reliable for diagnosis of EIB. B

Exercise-induced bronchoconstriction in the athlete may be accompanied by symptoms of cough, wheeze, chest tightness, shortness of breath, or excessive mucous production. However, a clinical diagnosis of EIB based on self-reported symptoms after exercise alone may be misleading because often objective measures cannot confirm asthma as the cause of the

symptoms.[1] Likewise, absence of self-reported symptoms also may be misleading because this could reflect lack of patient perception of EIB. Approximately half of elite winter sport athletes who report symptoms with exercise have normal airway function, and approximately half of those who report no symptoms will demonstrate bronchoconstriction after exercise or other indirect challenges.[1] This study documents the necessity of objective spirometry using a standardized protocol for diagnosis of EIB. Another investigation[2] corroborated that symptoms were not predictive of EIB in a study of college students. Using EVH with a 10% or greater decrease in FEV_1 to diagnose EIB, this study[2] identified a prevalence of 36% in those with no symptoms and 35% in those reporting symptoms of EIB. Athletes with high ventilation activities were significantly more symptomatic (48%) than athletes in low ventilation sports (25%; $P = .02$) but showed no difference in EIB prevalence between the groups when challenged. It is therefore essential to confirm EIB by objective measures generally following FEV_1 by using standardized tests.[3]

Summary Statement 18. Optimal EIB management may require confirmation of the diagnosis using objective methods. A

Although there is no single test that will identify all individuals who have EIB, indirect challenges, including exercise, EVH, inhaled powdered mannitol, nebulized hypertonic saline, or AMP, are more effective in identifying EIB than are direct challenges such as histamine or methacholine.[18,245–247] In addition, indirect challenges are recommended[3] for monitoring asthma therapy because BHR is most often related to inflammation and inflammation is diminished by ICS treatment for asthma.

The indirect challenges release mediators of inflammation, including LTs, PGs, and histamine, that provoke airway smooth muscle contraction.[13] Therefore, indirect challenges may reflect the severity of airway inflammation.[247] In contrast, direct challenge agents act directly on airway smooth muscle receptors to provoke bronchoconstriction, exclusive of airway inflammation.[3]

Challenges with pharmacologic agents that act directly on airway smooth muscle such as methacholine may be performed in the office, clinic, or hospital laboratory. These challenges are usually recommended to exclude a diagnosis of asthma rather than to exclude or include a diagnosis of EIB; however, they may be the only tests available. The direct challenge requires inhaling increasing concentrations of methacholine and then performing FEV_1 but not the full FVC maneuver after the administration of each dose. A decrease in FEV_1 of greater than 20% from baseline is regarded as a positive challenge result. This is documented as the PC_{20}. A PC_{20} of greater than 16 mg/mL is interpreted as normal bronchial responsiveness, between 4.0 and 16 mg/mL is considered borderline BHR, between 1.0 and 4.0 mg/mL is considered mild BHR (positive test result), and a less than 1.0 mg/mL is considered moderate to severe BHR.[6] Although the direct challenge is used as a screening test for chronic asthma, it has low sensitivity for EIB because it reflects the effect of only a single agonist and is not recommended as a screening tool for EIB.[4,246]

Exercise Challenge

The lack of strict adherence to the components of the consensus statement published by the ATS[6] on a standardized exercise challenge for EIB has led to variability in documented prevalence of EIB.[35] Diagnosis by exercise should be made by using a challenge that is standardized for duration of exercise and for intensity by standardizing minute ventilation and water content of inhaled air.[17,49,53,54,248,249] Spirometry is performed at baseline before the exercise challenge and at a series of defined postchallenge times, such as often as 1 to 3, 5, 10, 15, 20, and 30 to 45 minutes after 8 minutes of exercise, with 2 repeatable FEV_1 efforts (and not full FVC maneuvers) at each time point. The goal is to collect spirometry data as early and as late as practical within the time in which EIB typically occurs.[3] For example, the IOC-MC Independent Panel on Asthma recommends that FEV_1 should be first recorded at 3 minutes after the completion of the challenge to overcome the problem of possible posttest respiratory muscle fatigue. Post-exercise FEV_1 values are compared with preexercise FEV_1 values to calculate a percentage change from baseline. A 10% or greater decrease in FEV_1 from an FVC or FEV_1 maneuver at any 2 consecutive time points within 30 minutes of ceasing exercise may be considered diagnostic of EIB.[6] If a greater decrease in FEV_1 is required (ie, a decrease of 25%), then only one time point may be necessary to be diagnostic of EIB. In any case, it is important to examine the AUC to determine whether the decrease is consistent and is not likely an artifact of an inadequate spirometry effort.

A flattened or truncated inspiratory loop and a decrease in FEV_1 with no alteration in the FEV_1/FVC ratio are consistent with, but not diagnostic of, VCD.[250,251] However, the absence of this finding does not rule out VCD as described below. The presence of stridor suggests upper airway dysfunction with or without the concomitant presence of EIB. If VCD is a consideration, then FVC maneuvers should be used to compare preexercise and immediate postexercise inspiratory loops.

Expert panels and reports from experts have developed consensus guidelines for diagnosis of EIB based on exercise challenges.[6,252,253] Panels have suggested that the postexercise decrease in FEV_1 required to make the diagnosis must be 10%, whereas other groups have suggested that a decrease of 13% or 15% is necessary to make the diagnosis.[37,253] A 15% decrease in FEV_1 after a "field" exercise challenge[40] and 6% to 10% decrease in FEV_1 for laboratory challenges have been recommended.[171,226] Although there is no absolute standard cutoff postexercise decrease in FEV_1, the change in FEV_1 after exercise is normally distributed. Lowering the cutoff will result in an increased likelihood of false-positive test results for EIB, whereas raising the cutoff will result in the increased likelihood of false-negative test results for EIB. The ATS[6] and the European Respiratory Society[99] have rec-

ommended a 10% decrease in FEV_1 after exercise as criterion for EIB, based on 2 standard deviations from the mean percentage decrease in FEV_1 in healthy individuals.[38]

As noted above, it is essential to confirm the diagnosis of EIB using objective measures because of the lack of sensitivity and specificity of self-reported symptoms. The exercise challenge for diagnosis of EIB can be sensitive and specific if exercising minute ventilation and water content of inhaled air are standardized.[248,249] Standardized laboratory-based EIB challenges have been performed using 6 to 8 minutes of exercise in ambient conditions (20°C-25°C, relative humidity [RH] <50%) at 80% to 90% of estimated HR_{max} as a surrogate standard to V_E.[254–258] Maximal heart rate is often estimated by the equation of 220 − age; however, more recent analysis suggests that a more accurate regression equation to predict HR_{max} is 208 − 0.7 × age.[259] Ideally, the exercise ventilation should be above 60% of predicted maximum (ie, greater than 21 times FEV_1).[6] Some investigators have suggested that exercise intensity should be less than 85% of predicted HR_{max}[260]; these recommendations are based on the inappropriate assumption that exercise intensity affects catecholamine release and causes bronchodilation. This assumption is most invalid for individuals who routinely exercise because 85% HR_{max} may not be adequate to elicit a bronchoconstrictive response. Although ATS guidelines[6] and investigations by others[17,224,252,256–258] suggest that laboratory-based EIB testing should include an exercise challenge of 6 to 8 minutes in ambient conditions (20°C-25°C, RH <50%) at 80% to 90% predicted HR_{max}; very well-conditioned individuals may require the exercise intensity to be above a HR_{max} of 90%. Investigators[17] evaluated the exercise load in relationship to EIB severity in children (aged 9–17 years old) with asthma and found that treadmill tests at 85% and 95% of calculated HR_{max} resulted in greatly different decreases in FEV_1 (Figure 2). Decrease in FEV_1 was 25.1% at 95% HR_{max} but only 8.8% at 85% HR_{max}. Only 9 of 20 individuals had decreases greater than 10% at 85% HR_{max}, whereas all 20 individuals had decreases greater than 10% at 95% HR_{max} (Figure 2). This investigation supports the necessity for a high exercise intensity, which elicits high V_E.

Dry air delivered by the use of Douglas bag, as described below in the "Laboratory Challenges" section, also may enhance the ability to achieve a positive challenge because a dehydrating stimulus is thought to be a primary trigger of EIB. However, increased vagal activity from facial cooling during cold air exercise[261,262] or after water emersion[263] has been shown to result in significant bronchoconstriction in healthy individuals and asthma patients. It has been demonstrated that facial cooling during exercise resulted in significantly lower FEV_1 after exercise with either cold or warm dry air inhalation than did similar exercise without facial cooling.[261]

Field-Based Challenges

Free running[40,226,253] and sports-specific exercise challenges[162–164,230,264] have been shown to be valid for the evaluation of EIB. These challenges have been demonstrated to be more sensitive than laboratory challenges at ambient temperature and RH in the laboratory in elite winter athletes.[226] One study[226] compared sports-specific field-based exercise challenges of varied duration to a standardized 6- to 8-minute laboratory exercise challenge. Laboratory conditions were 21°C, 60% RH, and exercise intensity of 95% of peak heart rate. Although 5 athletes were positive by both challenges, 18 of 23 athletes who tested positive for EIB by field-based challenge tested normal by the ambient condition laboratory challenge (Figure 3). These results provided strong support for the notion that water content of inhaled air is a primary stimulus for EIB. Sport-specific tests have been used with success by researchers[164] who studied winter Olympic athletes participating in Nordic skiing, speed skating, ice hockey, and ice skating to evaluate EIB, as did another group of researchers[264] who used a 15-minute Nordic ski field exercise to identify EIB in cross-country skiers. Free running has been used to screen large populations of individuals because of the ease of administration. Several groups have used free running to evaluate schoolchildren.[40,237,253,265] Good validity and reliability of a free run test to evaluate airway responsiveness in large groups of children 8 to 11 years of age have been established; a 15% decrease in FEV_1 was used

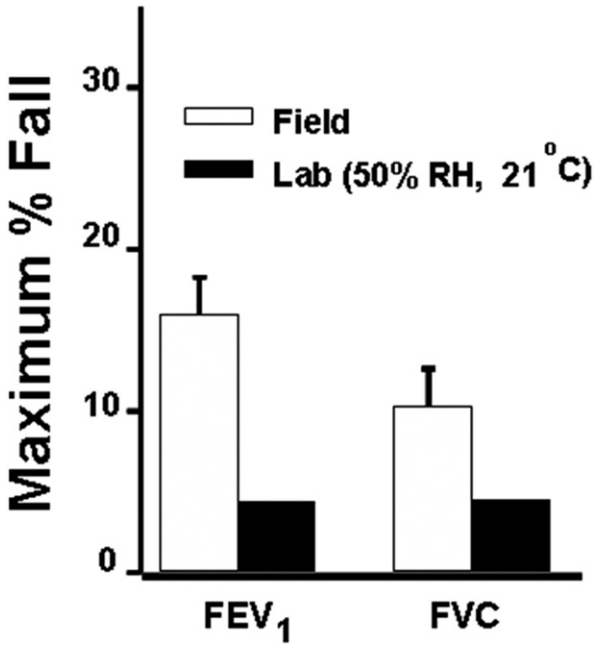

Figure 3. Of 23 elite winter athletes who tested positive for exercise-induced bronchoconstriction by a sports-specific field-based exercise challenge in cold dry air, only 5 (approximately 22%) tested positive by a laboratory treadmill run of equal intensity but under ambient conditions of 21°C, 50% relative humidity (RH). This figure displays data from the 18 athletes who tested negative by laboratory challenge. Adapted from Rundell et al.[226] FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity.

as cutoff criteria,[253] and the 95% probability for repeated tests was a ±12% decrease in FEV_1.[40,253] Researchers[37] also evaluated 8 studies with 232 young asthma patients and determined that a decrease in FEV_1 of 13% after exercise provided a sensitivity of 63% and a specificity of 94%, thus providing objective data to evaluate bronchial provocation challenge results. Furthermore, the cutoff value was not affected by the severity of asthma. However, the uncontrolled nature of the stimulus and changing ambient and environmental conditions impose variability that may limit free run tests as a means of monitoring therapy. A more reproducible stimulus and physiologic outcome may be needed to monitor treatment effectively.[3]

Laboratory Challenges

The laboratory exercise challenge for EIB can have high specificity and high sensitivity when standardized. The water content of inspired air should be below 5 $mg \cdot L^{-1}$ of air.[51,59] Because a primary trigger for EIB is the increase in osmolarity of the periciliary fluid, secondary to loss of water due to conditioning of relatively dry inspired air during exercise or hyperventilation,[12,52] the level of minute ventilation achieved and maintained should be approximately 60% to 85% MVV.[226] As noted above, this can be estimated by multiplying the baseline FEV_1 by 21 and 30, respectively.

Others have demonstrated a 50% reduction in severity of EIB when comparing exercise challenge conditions of 40% and 95% RH at ambient temperature (24% vs 12% decreases in FEV_1, respectively).[266] Others[248,249] examined inhaled airway temperature and EIB response and noted that severity of EIB was related to water content and not air temperature per se during exercise or EVH challenges. In these studies,[248,249] subjects exercised or performed EVH while breathing room temperature (22°C) or cold (−1°C) dry air, with water content for both conditions less than 5 mg/L of air; exercising minute ventilations were not different among conditions. No significant difference in postexercise FEV_1 between inhaled room temperature and cold air conditions was found. Similarly, there was no difference between exercise and EVH with matched minute ventilations (Figure 4).

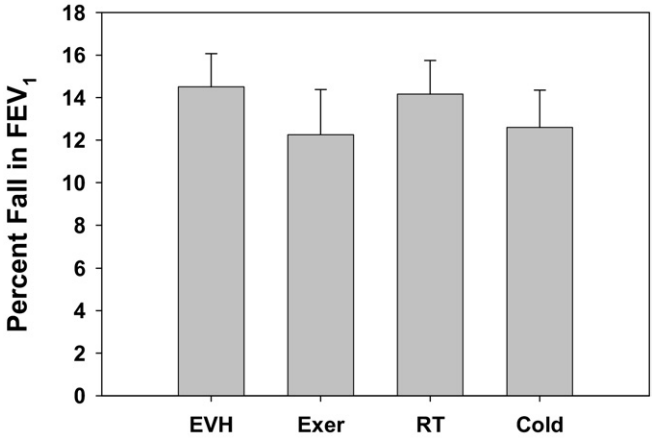

Figure 4. Athletes with mild exercise-induced bronchoconstriction underwent exercise (Exer) and eucapnic voluntary hyperpnea (EVH) challenges breathing either cold (Cold) or room temperature (RT) dry air. The first bar is all EVH (Cold and RT), the second bar is all Exer (Cold and RT), the third bar is all RT (EVH and Exer), and the fourth bar is all cold (EVH and Exer). Similar decreases in FEV_1 were seen for combinations of both challenge modes and both temperature conditions with no significant differences being observed. Adapted from Evans et al.[249]

Treadmill or Cycle Ergometer Exercise Challenge

Current recommendations indicate that an 8-minute exercise challenge that approaches 90% or more of estimated HR_{max} by 2 minutes and is maintained for the remaining 6 minutes of the 8-minute challenge is optimal for identifying EIB. A shorter duration of 6 or 7 minutes is often used in children. This protocol should ensure a minute ventilation of approximately 60% to 85% of MVV, with the exceptions of the elite athlete for whom a higher intensity may be required or the asthmatic patient who may not be able to achieve the high ventilation. For the elite or highly conditioned athlete, an intensity of approximately 95% HR_{max} is recommended. Exercising target minute ventilation can be estimated by multiplying the baseline FEV_1 by 21 and 30 times for 60% and 85% MVV, respectively.[94,169,267]

Treadmill Protocol. The treadmill speed and incline are selected according to the tester's subjective assessment of the individual's physical fitness with the ultimate goal of obtaining a total test duration of 8 minutes with the final 4 to 6 minutes at an intensity equal to 80% to 90% of estimated HR_{max}. This intensity should result in a ventilation equal to 40% to 60% of MVV.[6] A reasonable protocol is to begin the test at 2.5 mph (4 kph) at an incline of 2.5%, adjusting speed and incline to elicit a heart rate of 80% to 90% HR_{max} within 2 minutes and maintain it for the remaining duration of the 8-minute challenge.[39] There are nomograms that can be used to estimate oxygen consumption in relation to body weight and treadmill speed both for children[268] and adults.[269] Patients can terminate the challenge at any time during the test if they feel unable to continue.[28] Because water content and minute ventilation are major determinants of the severity of the decrease in FEV_1, it is important to increase the minute ventilation rapidly. Thus, protocols using progressive exercise such as the Bruce Protocol and the Jones Progressive Exercise Protocols[270] are inadequate to evaluate EIB because they do not increase the minute ventilation fast enough and may lead to refractoriness without provoking a decrease in FEV_1. Unfortunately, ventilation is the stimulus, but it is not usually measured because of equipment limitations.

Bicycle Ergometer Protocol. The designated workload of the bicycle ergometer challenge is based on the relationship between oxygen consumption and workload, as well as between ventilation and FEV_1.[271] For example, for a patient with predicted FEV_1 of 3 L, the target workload would be 150 W.

As described by 2 sets of authors,[6,271] the test begins at 60% of target workload (eg, 90 W) for the first minute, then 70% (105 W) and 90% (135 W) for second and third minutes, and 100% (150 W) for minutes 4 to 8. This equation has some limitations and only acts as a guide for a target workload. For some patients, it may generate a workload that is too high, yet for others it may be too low so adjustments may be needed during exercise.

Inhaled air during both challenges should be dry medical-grade air (<5 mg H_2O+L) administered via a gas cylinder with a reservoir bag (Douglas bag) and 1-way valve apparatus; nose clips should be worn during the test. It is recommended that the challenge is not performed while breathing ambient air (eg, 22°C, 50% RH) because of the increased likelihood of a false-negative test result.[226] Heart rate, arterial oxygen saturation by pulse oximetry, and minute ventilation (if possible) should be measured throughout the test; heart rate and arterial saturation should be monitored after challenge to recovery. Monitoring of oxygen saturation is of primary importance in the differential diagnosis of exercise-induced hypoxemia (EIH). Exercise-induced hypoxemia, a significantly compromised gas exchange during heavy exercise, affects approximately 40% of elite endurance athletes[272] and is commonly misdiagnosed as EIB. Tight control of test conditions enhances high test-retest reliability important for monitoring patient treatment on subsequent follow-up.[271] Either cycle ergometry or treadmill running is an acceptable mode of challenge; however, careful monitoring of cycle load or treadmill running speed and elevation is important to test validity and reproducibility. The most important determinants of the response to exercise are the ventilation achieved and sustained for 6 to 8 minutes and the water content of the inspired air; thus, the ventilation should be considered the measure of the stimulus when dry air is inspired and heart rate as only a secondary means of monitoring the intensity of the stimulus.

Pulmonary function tests should follow ATS standards for FEV_1 and FVC maneuvers.[6] Two reproducible efforts with FEV_1 within 3% of each other should be obtained before the exercise challenge; the best effort should be used to calculate postexercise decrease in FEV_1. Before conducting the exercise challenge, it is useful to calculate some target values from the preexercise FEV_1; for example, the FEV_1 value that represents (1) a positive test result (ie, a 10% decrease in FEV_1), (2) an alert for severe bronchoconstriction and need for administering a bronchodilator (ie, 50% decrease in FEV_1), and (3) an indication of recovery (ie, the 95% value for recovery of FEV_1). Two reproducible expiratory efforts should be obtained after exercise usually at 1 to 3, 5, 10, 15, 20, and perhaps 30 to 45 minutes after completion of the challenge or at least until the nadir in FEV_1 is reached and recovery has started. A positive test result is best confirmed by a 10% decrease in FEV_1 from baseline at 2 consecutive time points. Full follow-up of FEV_1 to recovery permits the maximal decrease in FEV_1 to be identified. This value is useful for identifying benefit of a medication because a 50% reduction in the decrease after treatment is considered a significant benefit. Further follow-up of FEV_1 for 60 minutes allows the calculation of area under the FEV_1 time recovery curve ($AUC_{0-60\ min}$) and permits calculation of the time to 95% recovery in FEV_1. The patient should remain at the office or laboratory until the FEV_1 has returned to 95% of baseline value or the clinician feels that it is safe for the patient to leave the clinic.

Eucapnic Voluntary Hyperpnea Challenge

Eucapnic voluntary hyperpnea was developed and standardized at the Walter Reed Hospital in Washington to assess EIB in recruits with a history of asthma.[273] Eucapnic voluntary hyperpnea was later identified as a useful test to identify EIB in elite athletes who were often limited by the lack of an appropriate ergometer that would challenge them sufficiently.[4,94,274] Eucapnic voluntary hyperpnea has since been recommended by the Independent Panel on Asthma of the IOC-MC as the optimal test to identify EIB for athletes seeking approval to inhale a β_2-agonist before an event.[165,169]

The profile of the airway response to EVH shares many similarities with exercise. This includes the stimulus itself, the time course of the airway response and the recovery, the mediators involved, and the inhibitory effects of drugs.[30,32,97,114] However, EVH does not result in the same cardiovascular response as exercise or the same sympathetic drive, and there are a few subjects who test negative to EVH but positive to exercise.[93,94]

An EVH challenge requires the subject to breathe dry medical-grade air (containing 4.9%–5% carbon dioxide, 21% oxygen, and balance nitrogen) at an exercising V_E for 6 minutes. Because hyperventilation-induced hypocapnia can cause bronchoconstriction in people with and without asthma,[275] eucapnia should be ensured by using EVH air mixture containing 5% carbon dioxide.[94,274,276] It has been demonstrated that a single fraction of inspired carbon dioxide (4.89%) will provide near normal alveolar carbon dioxide over a wide range of voluntary hyperventilation (30–110 L/min).[91] This may not be applicable to the elite athlete. This was a primary study that demonstrated that the EVH challenge produced similar decreases in FEV_1 to a dry air exercise challenge.

The general procedure for the EVH challenge involves voluntary breathing of the air administered through a 2-way valve connected to a gas cylinder through a reservoir bag for 6 minutes. Prechallenge and postchallenge spirometry are performed. Recommended ventilation rate for EVH is between 21 and 30 times FEV_1 (representing 60% and 85% MVV, respectively). A target value of 30 times FEV_1 is best used only for trained or elite athletes who regularly perform exercise without premedication. The lower value of 21 times FEV_1 is used in known asthmatic patients or those with a history of EIB not taking regular treatment. Patients may have suboptimal challenges when lower levels of ventilation are used as the target.[97] The ventilation reached and sustained are important determinants of the response to exercise.[13] However, prolonged periods of hyperpnea can result in a significant refractoriness to the stimulus; it has been demon-

strated[277] that 2 consecutive EVH challenges within 93 minutes resulted in respective decreases in FEV_1 of 27.4 ± 9.8 and 16.1 ± 5.9, whereas three 2-minute interrupted EVH challenges resulted in an 18.9 ± 10.6 decrease in FEV_1 after the last challenge.[277]

It is important to measure minute ventilation to ensure adequate and consistent ventilation throughout the 6-minute test. This can be accomplished by using either a rotameter between the gas cylinder and patient to maintain a constant predetermined flow and/or by measuring continuous V_E on exhalation. One variation of EVH is to chill inspired air, which has been hypothesized to lead to a greater change in airway osmolarity or vascular response. However, others[248,249] found no difference in postEVH decreases in FEV_1 when the room temperature or cold air was inhaled (Figure 4). Because the cold temperature inhaled air did not have an additive effect on the bronchoconstrictive response, the same authors[248,249] confirmed earlier work[70] demonstrating that water content, and not temperature of inhaled air, is the essential test condition from bronchoconstrictive response. It must be reiterated that EVH should be performed with caution in individuals who have a baseline FEV_1 less than 80% of predicted and should not be performed in those with baseline FEV_1 less than 70% of predicted.

Hypertonic Saline Challenge

The hypertonic saline challenge is economical and an easily administered indirect challenge that increases ASL osmolarity and triggers sensitized cells to release inflammatory mediators.[278–280] There are many similarities among challenges with hypertonic saline, EVH, and exercise.[281,282]

In addition, hypertonic saline allows for concurrent collection of sputum samples for mediator and cellular analysis.[283–285] The hypertonic saline (4.5%) aerosol is generated using a high-output ultrasonic nebulizer and the exposure times are progressively increased (ie, 30 seconds, 60 seconds, 2 minutes, 4 minutes, and 8 minutes, which together totals 15.5 minutes) so that the total test time is usually less than 20 minutes; moreover, decreases in FEV_1 are usually not severe.[283–285] Initial exposure to the 4.5% hypertonic saline lasts for 30 seconds[284]; this interval is doubled if FEV_1 decreases less than 10% between exposures. Forced expiratory volume in 1 second is measured 60 seconds after exposure. If FEV_1 decrease is 10% or more, the exposure time is repeated; the test is terminated if decrease is 15% or more in FEV_1 or when a total dose of 23 g has been administered in 15.5 minutes.[284] Inhaled saline produces a dose-dependent response, allowing for classification of the severity of BHR in populations of those not using ICS. An epidemiologic study[279] found that children positive to hypertonic saline were approximately 4.26 times more likely to have EIB. A later study by the same investigators corroborated a positive response to saline and diagnosis of asthma.[286]

Thus, hypertonic saline has been used to identify the potential for BHR in patients with a history of asthma who are currently symptomatic[287] and asymptomatic.[288] This is particularly useful in those who wish to participate in scuba diving because 18% of intending scuba divers have been shown to have asthma and hypertonic saline is useful to assess the effect of treatment.[289]

Inhaled Powder Mannitol Challenge

Mannitol is a stable sugar alcohol found in most vegetables that is a hyperosmolar agent that has been developed into a bronchial provocation challenge.[290] The mannitol test is approved in Europe, Asia, Australia, and the United States for the assessment of bronchial hyperresponsiveness.[3] Like exercise, EVH, and hypertonic saline, inhaled powder mannitol is an indirect challenge that produces airway smooth muscle contraction by creating a hyperosmolar environment that leads to release of mediators from inflammatory cells of the airways.[81] Mannitol challenge is associated with mast cell activation and mediator release; after mannitol challenge, the levels of urinary $9\alpha,11\beta PGF_2$, and LTE_4 were increased similarly in both asthmatic and nonasthmatic subjects.[81] The results of this study suggest that the difference between asthmatic and nonasthmatic subjects is not in the release of mediators per se but more in the responsiveness of airway smooth muscle to bronchoconstrictive mediators. As an indirect challenge, inhaled powder mannitol reflects the neural and cellular aspects of the airway responsiveness rather than just smooth muscle hyperresponsiveness independent of mediator release.[283,290]

Mannitol is administered from a dry powder inhaler device in progressive doubling doses of 5, 10, 20, 40, 80, 160, 160, and 160 mg, with a maximal total dose of 635 mg, depending on the airway response.[39,290] One minute after each dose, FEV_1 is measured in duplicate by the FEV_1 maneuver. Full FVC maneuvers should not be obtained to avoid tiring patients who are performing any of these tests and to avoid taking too long to perform spirometry. The baseline FEV_1 obtained after the initial capsule containing no mannitol is used to calculate the target for the 15% decrease in FEV_1 ($0.85 \times$ 0-mg dose FEV_1) after subsequent doses. The challenge is discontinued when there is a 15% or greater decrease in FEV_1 from baseline or a between dose decrease of 10% or greater in FEV_1 or a cumulative dose of 635 mg is administered.[39] The data are expressed as the dose required to provoke a 15% decrease in FEV_1 (PD_{15}), which is obtained by plotting the change in FEV_1 against the log cumulative dose of mannitol delivered. The following equation[6] is used to calculate the PD_{15}:

$$PD_{15} = \text{antilog}\left[\log D_1 + \frac{(\log D_2 - \log D_1)(15 - F_1)}{F_2 - F_1}\right]$$

where D_1 is the mannitol dose preceding D_2, D_2 is the final mannitol dose resulting in a 15% or greater decrease in FEV_1, F_1 is the percentage decrease in FEV_1 after D_1, and F_2 is the percentage decrease in FEV_1 after D_2.

The inhaled powder mannitol challenge has a number of inherent advantages over other indirect and direct challenges.

It is practical for office administration because of the ease of use, short time to perform the challenge, and no requirement for specialized and costly equipment, such as a treadmill or cycle ergometer. The only requirements are spirometer, nose clips, calculator, and mannitol kit.

There is a significant relationship between sensitivity to mannitol and reactivity to exercise in known asthmatic patients not being treated with inhaled steroids.[247,291] Mannitol as a challenge test has also been used to identify EIB in elite athletes.[292] There is a lower sensitivity for mannitol to identify EIB in those with symptoms but no definite diagnosis of asthma.[39] Mannitol has been used successfully to identify BHR in individuals with exercise-induced wheeze.[293]

Of potential importance is the capability to use the mannitol challenge to document treatment effectiveness.[294] Because BHR is dependent on the presence of airway inflammation, a decrease in sensitivity to mannitol may be used as an index of reduction in airway inflammation. This can be documented by change in PD_{15} and RDR (calculated by dividing the final percentage decrease in FEV_1 by the cumulative dose of mannitol producing that decrease). There was a significant reduction in sensitivity (PD_{15}) and airway reactivity (RDR) in asthmatic patients after treatment with ICS; the PD_{15} increased from a pretreatment value of 78 mg to 289 mg after treatment and a 4.2-fold improvement in RDR.[294]

Summary Statement 19. Self-reported symptom-based diagnosis of EIB in the elite athlete lacks sensitivity and specificity and establishes the necessity for standardized, objective challenges using spirometry. B

The elite athlete with EIB typically presents with symptoms of cough, wheeze, chest tightness, dyspnea, and excess mucus.[1] However, the same symptoms may be present in elite athletes without reversible airway obstruction, and the athlete may not be adept at reporting those symptoms.[1,2] Investigators[1] demonstrated that approximately half of elite athletes who reported EIB symptoms had normal spirometry after a challenge test and approximately half who reported no symptoms of EIB tested positive. Others[2] demonstrated essentially the same results in Division I college athletes. These data demonstrate that the diagnosis of EIB in the elite athlete must be confirmed with a positive challenge test result.

Summary Statement 20. The indirect challenge (eg, exercise or surrogate such as EVH) is preferred over a direct challenge (eg, methacholine) for assessing EIB in the elite athlete. D

Challenge tests for asthma and EIB are either direct or indirect. The direct challenge involves methacholine or histamine inhalation and acts on smooth muscle receptors in the muscle. This challenge is independent of airway inflammation. The direct challenge involves inhalation of methacholine or histamine in progressively increasing amounts until a decrease in FEV_1 of 20% or greater from baseline occurs. If a PC_{20} of methacholine is less than or equal to 4 mg/mL when the patient is not taking ICS or 4 to 16 mg/mL when the patient has been taking ICS for 1 month or longer, the test result is considered positive according to the IOC-MC.[295]

The methacholine challenge is not recommended for the athlete with EIB without the presence of known asthma. Methacholine has been shown to have a low sensitivity and high specificity for EIB without asthma.[206] A study examining 50 elite summer athletes[4] found that 42 reported 1 or more symptoms, 9 had positive methacholine challenge results, and 25 had positive EVH challenge results with a mean decrease in FEV_1 of 25.4% $\pm$ 15%. Methacholine had a negative predictive value of 61% and a sensitivity of 36% for identifying athletes responsive to EVH.

Summary Statement 21. Eucapnic voluntary hyperpnea is the preferred surrogate challenge for the elite athlete participating in competitive sports. D

Indirect challenges are preferred for assessing EIB in elite athletes. The most frequently used indirect challenges for elite athletes include sports-specific field exercise, laboratory exercise, EVH, and inhaled powder mannitol. Eucapnic voluntary hyperpnea is considered the most useful and predictive of these indirect challenges,[2,4,94,236,274,296] and because of the high sensitivity to identifying athletes with EIB, it is the challenge recommended by the IOC-MC Independent Asthma Panel.[295] Sports-specific field-based exercise challenges at race-pace intensity are successfully used,[164] but the lack of environmental control affects results and test-retest consistency.[3] Using competitive swimmers as subjects, an investigation[236] demonstrated that a sports-specific challenge was not effective at diagnosing EIB in swimmers. Eucapnic voluntary hyperpnea was more likely to produce a positive response than a swim challenge or a laboratory cycle challenge at more than 85% estimated HR_{max}, temperature of 21°C, and RH of 50%; 1 of 33 subjects had a positive field swim challenge result, 18 had a positive EVH challenge result, and 4 had a positive laboratory cycle challenge result.

Ventilation for EVH should be at more than 85% MVV when testing the elite athlete, and inhaled air contains less than 5 mg H_2O/L of air. The EVH test uses compressed air with 4.95% to 5% carbon dioxide to ensure eucapnia, as described earlier, and the test should be of a 6-minute duration and follow the procedure previously described. The EVH test should be performed with caution, especially in patients with FEV_1 that is below 80% of predicted, and should not be performed on patients in whom FEV_1 is less than 70% of predicted.

Summary Statement 22. The intensity of the exercise challenge for the elite athlete should be 95% or greater than actual or estimated HR_{max}, and dry medical-grade air should be used in performing the challenge. D

Laboratory exercise challenge should follow the same procedures as described earlier; however, exercise intensity should be at or above 95% of HR_{max} for the last 4 minutes of the 8-minute test. This heart rate–based intensity will ensure adequate ventilation for a reliable test. Cycle ergometry tests should be reserved for athletes who are cyclists, skaters, or alpine skiers, whereas treadmill run tests should be performed on Nordic skiers and runners. Triathletes can be tested by cycle ergometry or treadmill running. Although cutoff criteria

have been shown to be statistically justified at values less than a 10% decrease in FEV_1,[1,231] the IOC-MC dictates a 10% or greater decrease in FEV_1 3 to 30 minutes after exercise as a positive challenge result.

Summary Statement 23. Hyperosmolar aerosols may also be used as surrogates to exercise. C

Inhaled mannitol has been successfully used as a challenge surrogate for EIB in elite athletes.[292] A decrease in FEV_1 of 15% or more after inhaling 635 mg of dry powdered mannitol is considered positive for EIB. The mannitol response is reported as PD_{15} or a between dose fall of 10%,[39] and these challenges are supported by the IOC-MC.[35,169]

In conclusion, a diagnosis of EIB must include objective lung function measures using a standardized indirect challenge. Although the standardized dry air exercise challenge and EVH are effective in diagnosing EIB, equipment is expensive and may not be practical in many clinical settings. Nevertheless, the hypertonic saline challenge and inhaled powdered mannitol require less equipment and space and can be easily performed in the office environment.

Differential Diagnosis

Summary Statement 24. Exercise-induced laryngeal dysfunction, primarily VCD and other glottic abnormalities, may be elicited by exercise and mimic EIB. Inspiratory stridor is a differentiating hallmark sign with EILD and not with EIB alone. Flattening of the inspiratory curve on spirometric maneuver may be seen concomitant with symptoms. Exercise-induced laryngeal dysfunction may occur alone or with EIB. Failure to respond to asthma management is a key historical feature suggesting EILD. C

Since the initial description of VCD as a functional disorder that mimicked attacks of asthma,[297] VCD and glottic structural abnormalities elicited seen with exercise have been increasingly recognized. These functional and structural disorders can be grouped as EILD, including (1) paradoxical VCD, (2) exercise-induced laryngeal prolapse,[298] (3) exercise-induced laryngomalacia,[299] and (4) variants, including arytenoid collapse while the vocal cords move normally.[300] Exercise-induced laryngeal dysfunction occurs in all age groups, especially among young adult female elite athletes.[250]

Bronchial provocation challenge with methacholine, exercise, and EVH may be negative in patients with EILD who do not otherwise have BHR. The onset of breathing difficulties occurs and peaks during exercise with EILD, rather than peaking after exercise with EIB. Medications used to treat asthma such as β_2-agonists are ineffective to prevent or reverse EILD. Exercise-induced laryngeal dysfunction can be suspected by bronchial provocation challenges with isocapnic hyperventilation of frigid air, methacholine, and/or exercise demonstrating variable extrathoracic airway obstruction.[301]

Inspiratory stridor with throat tightness during maximal exercise resolves within approximately 5 minutes of discontinuation of exercise in patients with EILD. Inspiratory stridor with EILD contrasts with EIB, in which case dyspnea generally occurs after exercise, peaks 5 to 20 minutes after stopping, and involves expiration rather than inspiration.[7] There may be variations in the timing of the manifestation of EILD symptoms, depending on such factors as the duration and intensity of the exercise.

In VCD, direct observation of the vocal cord adduction by laryngoscopy and flattening or truncation of the inspiratory portion of the spirometric flow-volume loop are the hallmarks for diagnosis. These findings may only be seen during symptomatic periods. Methacholine challenge can be used to elicit VCD.[302,303] Additional evidence of VCD may be suggested by examining a video of the patient recorded while exercising in the natural setting at the time that inspiratory stridor is heard.[304] Diagnosis can be made directly by using continuous laryngoscopy during exercise challenge.[305] Spirometry and laryngoscopy with sound recording can be performed during exercise, detecting minor and major aryepiglottic and vocal cord abnormalities.

Exercise-induced laryngeal prolapse has been seen in otherwise healthy athletes and can present with subtotal occlusion of the larynx. This condition may result from mucosal edema from the aryepiglottic folds being drawn into the endolarynx (laryngochalasia).[298] Laryngoscopic evaluation at rest may be normal, and various laryngeal abnormalities may only be elicited with exercise challenge.[306]

Laryngomalacia is associated with diminished laryngeal tone, resulting in supraglottic collapse, and is usually a congenital condition.[307] Laryngomalacia is the most common cause of inspiratory stridor in infants[308] but may not manifest until later childhood with participation in competitive sports.[299,307,309–311] Although the typical anatomical features of congenital laryngomalacia (shortened aryepiglottic folds or retroflexed epiglottis) may not be seen, other presentations, such as profound arytenoid redundancy and prolapse, can be seen during nasolaryngeal endoscopy. As in infants with laryngomalacia, supraglottoplasty can improve late-onset disease.[307,308] Laryngomalacia can also be seen in adults.[312]

Concurrent laryngeal abnormalities may be seen in patients with VCD. Laryngoscopy may identify findings suggestive of GERD, chronic laryngitis, laryngomalacia, vocal cord motion impairment, nodules, and subglottic stenosis, especially in patients in whom exercise induces symptoms.[313] Exercise-induced laryngeal dysfunction may coexist with EIB. Inspiratory stridor is the signature clinical feature suggesting EILD rather than EIB.

Gastroesophageal reflux anatomical findings may be seen on laryngoscopy in children and adults with EILD, but whether they are causative or concomitant is difficult to establish. Empiric pharmacologic treatment of GERD in juveniles having VCD has been recommended because posterior laryngeal changes associated with GERD are common in juveniles with VCD.[314]

Although laryngopharyngeal reflux may be a contributing factor in many EILD cases, there is little objective evidence supporting this. The sensitivity and specificity of the laryngoscopic examination to diagnose laryngopharyngeal reflux is also controversial.[315] Although there may be a clinical

suspicion of laryngopharyngeal reflux, there is an absence of an objective "gold standard" to establish this diagnosis.

Summary Statement 25. Exercise-induced dyspnea and hyperventilation can masquerade as asthma, especially in children and adolescents. C

Chest discomfort perceived as dyspnea during vigorous exercise may be associated with hypocapnia from hyperventilation without bronchoconstriction, especially in children and young adolescents previously diagnosed as having and having been treated for EIB.[19,20,316–319]

It has been demonstrated that exercise-induced lactic acidosis is causally involved in the hyperventilation. However, lactic acidosis does not represent the only additional stimulus of ventilation during intense exercise. Sensory input from exercising muscles such as muscle afferents may also trigger hyperventilation.[320,321]

Idiopathic hyperventilation is a poorly understood condition in which patients have sustained hyperventilation, hypocapnia, and dyspneic drive.[322]

Summary Statement 26. Shortness of breath with exercise may be associated with underlying conditions due to obstructive lung disease, such as COPD, or restrictive lung physiology, such as obesity, skeletal defects (eg, pectus excavatum), diaphragmatic paralysis, and interstitial fibrosis. B

Dyspnea with exertion in some obese patients may not be a manifestation of EIB.[323] Idiopathic pectus excavatum may be associated with exercise symptoms, including chest pain, dyspnea, or impaired endurance. Even in the absence of clinical symptoms, restrictive lung defects and lower airway obstruction are common.[324,325]

Scoliosis has been associated with decreased exercise tolerance. Patients who have mild scoliosis may be asymptomatic at rest but with exercise may have decreased tidal volume, as well as hypercapnia and hypoxia.[326]

Although diaphragmatic paralysis has a predictable effect on lung function, the symptoms depend on the preexisting heart-lung diseases and may mimic various cardiorespiratory processes, including EIB.[327]

Patients with interstitial lung disease frequently have dyspnea with exercise. These patients' exercise limitations appear to be related to arterial hypoxemia and not respiratory mechanics. Their dyspnea is often fixed and reproducible.[328,329]

Summary Statement 27. Shortness of breath accompanied by pruritus and urticaria, with varying other systemic symptoms, suggests EIAna rather than EIB. C

Exercise-induced anaphylaxis is characterized by the exertion-related onset of cutaneous pruritus and warmth, generalized urticaria, and appearance of such additional manifestations as shortness of breath, upper respiratory tract distress, vascular collapse, and gastrointestinal tract symptoms. This must be differentiated from asthma, cholinergic urticaria, angioedema, and cardiac arrhythmias, which are recognized as exertion-related phenomena in predisposed patients but are distinct from EIAna.[330,331] There is variability in the reproducibility of EIAna symptoms given similar testing conditions.

Episodes of food-dependent exercise-induced anaphylaxis (FDEIAna) may or may not be dependent on ingestion of identifiable foods.[332,333] The cumulative effect of exercise and food ingestion may trigger the mediator release and anaphylaxis, whereas each of these triggers independently does not. Foods reported as predisposing factors range from shellfish, eaten 4 to 24 hours before EIAna, to seemingly benign foods, such as celery, eaten before or after exercise.[332,333] Skin testing with foods may be helpful in eliciting the trigger when history taking does not.[334] Serum tryptase measurements may help in confirming the diagnosis of EIAna.[335] FDEIAna occurs in both children and adults.[330–336]

Wheat gliadin has been identified as the cause of FDEIAna due to wheat.[337] It has been further determined that cross-linking between tissue transglutaminase and ω-5 gliadin-derived peptides increases IgE binding. The tissue transglutaminase becomes activated in the patients' intestinal mucosa, and large allergen complexes become capable of eliciting anaphylaxis.[338] Exercise and aspirin have been shown to increase the levels of circulating gliadin peptides in patients with wheat FDEIAna, suggesting facilitated allergen absorption from the gastrointestinal tract.[339]

Although skin testing to the specific foods, commercial or fresh food extracts, or crude gliadin is most used, measurement of IgE levels specific to epitope peptides of ω-5 gliadin or recombinant ω-5 gliadin may be useful as an in vitro diagnostic method.[339,340]

Food-dependent exercise-induced anaphylaxis can have a delayed onset for an unpredictable number of hours. It has therefore been suggested that, in such patients, exercise should be avoided 4 to 6 hours after specific food ingestion. In patients with wheat gliadin–associated EIAna, a gluten-free diet is recommended.[337,341]

Susceptible patients may be advised to take an antihistamine before exercise and should carry self-injectable epinephrine, which is the primary treatment for anaphylaxis.[341]

Summary Statement 28. In the absence of objective evidence of EIB, breathlessness with exercise, with or without chest pain, may be caused by cardiovascular, pulmonary, or gastroenterologic mechanisms other than asthma. Appropriate cardiopulmonary testing and/or referral to a cardiologist, pulmonologist, or gastroenterologist may be necessary. B

Although the incidence of cardiac-related dyspnea with exercise in young, healthy patients is minimal, it remains an important differential in EIB. Primary pulmonary hypertension (PPH) may occur in both adults and children. Patients with PPH may demonstrate peripheral airway obstruction, poor oxygenation, and early physiologic aerobic limits restricting exertion and, in children, documentation of significant reversibility of lower airway obstruction.[342–344] A case report documents how PPH can masquerade as asthma. Two adult nonsmokers presenting with wheezing, chronic cough, and irreversible obstructive lung disease were diagnosed as having adult-onset severe refractory asthma but actually had dilation of the central pulmonary arteries, compressing the mainstem bronchi.[345]

Congestive heart failure may present with dyspnea on exertion. Hyperpnea with exercise may occur without lung function impairment. Ventilation-perfusion mismatch in exercise may be enhanced with increased treatment of heart failure.[346]

Hypertrophic cardiomyopathy is well known to cause sudden death in young athletes, with an annual 1% mortality rate.[347] Patients may have dyspnea and chest pain that improve with β-blockers.[348]

Cardiac dysrhythmias may also cause dyspnea with exercise. Supraventricular tachycardia may cause EIB in children.[19] Young adults with complete heart block may have shortness of breath, dyspnea on exertion, syncope, dizziness, or fatigue.[349]

Vascular rings of the aorta are rare but may present as asthma. Spirometry in these patients reveals a decreased peak expiratory flow and truncation of the expiratory flow volume loop with normal FVC, FEV_1, and FEV_1/FVC. Chest radiographs are significant for a right aortic arch.[350]

Pulmonary arteriovenous malformations and disorders with right to left shunts may cause exercise-induced dyspnea due to hypoxemia, without associated bronchoconstriction. Hereditary hemorrhagic telangiectasia, atrial septal defects, ventricular septal defects, and Osler-Rendu-Weber syndrome are among the primary causes. Cardiopulmonary exercise testing, as differentiated from pulmonary testing for EIB, is an appropriate noninvasive tool to begin and guide the evaluation of these patients presenting as undiagnosed dyspnea. The evaluation may require procedures such as cardiac catheterization to further delineate the right to left shunt.[351,352]

Exertional dyspnea in symptomatic patients with COPD may be due to the combined deleterious effects of higher ventilatory demand and abnormal ventilatory dynamics but not temporally attributable to bronchoconstriction.[353] Patients with COPD may have evidence of small airway dysfunction with increased ventilatory requirements during exercise likely on a basis of greater ventilation and perfusion abnormalities. These abnormalities also involve changes in end-expiratory lung volume and breathing patterns that are more shallow and rapid than in a comparatively healthy cohort.

Summary Statement 29. Exercise-induced dyspnea is seen as a physiologic limitation in otherwise healthy active individuals without bronchospasm. C

Perhaps the most common reason for exercise-induced dyspnea in children is physiologic (poorly conditioned) limitation without bronchospasm or underlying disease.[19] Limits in exercise performance and respiratory system oxygen transport may occur in highly fit adults.[354] This may be due to flow limitation in intrathoracic airways because of narrowed, hyperactive airways or secondary to excessive ventilatory demands superimposed on a normal maximum flow-volume envelope. In addition, exercise-induced arterial hypoxemia occurs as a result of an excessively widened alveolar-arterial oxygen pressure difference. This inefficient gas exchange may be attributable in part to small intracardiac or intrapulmonary shunts of deoxygenated mixed venous blood during exercise. Finally, fatigue of the respiratory muscles resulting from sustained, high-intensity exercise and the resultant vasoconstrictor effects on lung muscle vasculature will also compromise oxygen transport and performance. Exercise in the hypoxic environment of even moderately high altitudes will greatly exacerbate the negative influences of these respiratory system limitations to exercise performance, especially in highly fit individuals.

Summary Statement 30. The association between EIB and GERD is controversial, and probably there is no relationship. A

Although there are reports of exertional gastroesophageal reflux in healthy individuals, most studies have demonstrated no significant correlations between GERD and EIB.[355–357] Although acid reflux may be common in EIB patients, many patients with exercise-related respiratory symptoms may be misdiagnosed as having asthma when they truly have exercise-onset GERD.[358] Some controversies exist in treatment of GERD and EIB. Symptoms of acid reflux related to running were relieved by proton pump inhibitor, but the respiratory symptoms of EIB were not relieved by proton pump inhibitors.[359] In contrast, other investigators have reported improvements in exercise-related breathing symptoms when patients were treated with proton pump inhibitors.[358]

Summary Statement 31. Psychological factors need to be considered in the differential diagnosis of EIB. D

Psychological factors may obfuscate the diagnosis in patients with apparent exercise intolerance. Scenarios such as individuals, particularly young women, complaining of shortness of breath while running without having stridor, wheezing, or relief with trial bronchodilators are not uncommon but may be vexing to the patients, their parents, and their physicians. Although VCD and EIH may have functional triggers, differentiating EIB requires subjective and objective assessment.[360] Mental stress may be one trigger factor where hyperventilation is seen in patients with asthma-like symptoms with negative asthma test results.[361] If objective testing does not reveal any bronchoconstriction or other physiologic explanations, then psychological etiology should be considered and addressed with the patient, which may involve a recommendation for psychological consultation.

Summary Statement 32. Dyspnea on exertion, which is prevalent in otherwise healthy, obese individuals, is not associated with EIB. C

Dyspnea on exertion is present in obese patients. This dyspnea has been strongly associated with an increased oxygen cost of breathing, without bronchoconstriction, in otherwise healthy obese women.[362] Exercise capacity has been variously reported as unchanged in obese females to being reduced at or near maximal effort.[363]

Summary Statement 33. Mitochondrial enzyme deficiency with myopathy is a rare cause of exercise limitation. D

Impaired oxidative phosphorylation in working muscle disrupts the normal regulation of cardiac output and ventilation relative to muscle metabolic rate in exercise.[364] Deficiencies of mitochondrial enzymes cause a number of severe neurologic syndromes in pediatric patients. Isolated myopa-

thies secondary to enzymatic deficiency have been recognized in adults and may be more prevalent than reported.[365,366]

Therapy

Introduction

Summary Statement 34. Frequent EIB in asthmatic patients suggests inadequate asthma control and requires patient reevaluation to determine the need for additional therapy. D

Exercise-induced bronchoconstriction is a reflection of BHR and, in asthmatic children and adults, ordinarily is due to underlying inflammation. Exercise-induced bronchoconstriction in these individuals, most of whom are not elite athletes, may represent inadequacy of overall asthma control.[33,207]

Summary Statement 35. Failure of appropriate pharmacotherapeutic agents to prevent EIB indicates the need to reevaluate the diagnosis. D

The goal of therapy for EIB is to prevent symptoms induced by exercise, to enhance overall control of asthma, and to ameliorate symptoms rapidly when they occur. Pharmacotherapeutic agents that are effective in controlling chronic asthma generally have bronchoprotective activity for EIB. If asthma is otherwise well controlled, bronchoprotective therapy is administered only as needed. This therapy may be delivered by inhalation or by oral administration minutes to hours before exercise, respectively. Nonpharmacologic therapies can also be helpful in preventing EIB when used alone or in combination with pharmacotherapy; these are described in the "Nonpharmacologic Therapy" Section.

Summary Statement 36. Several pharmacotherapeutic agents are effective when given for the prevention or attenuation of EIB. They differ in their mechanisms of action and overall effectiveness. In addition, there is both intrapatient and interpatient variability in responsiveness. A

Pharmacotherapeutic agents act to prevent or attenuate EIB by various mechanisms with different degrees of effectiveness. None of the available therapies completely eliminates EIB. Pharmacotherapy shifts the dose-response relationship to a more favorable position after exercise.[367,368] The efficacy of a given agent in protecting against EIB can vary at different times and among different individuals.

Summary Statement 37. Medications may differ in effectiveness over time because of variability of asthma, environmental conditions, intensity of the exercise stimulus, and tachyphylaxis. A

The variability of effectiveness within an individual may be due to changes in airway responsiveness over time, environmental conditions, and intensity of the exercise stimulus.[369] The variability among individuals may result from differences in baseline airway responsiveness and susceptibility to tachyphylaxis and perhaps to genetic differences.[7] Pharmacotherapeutic studies supported by pharmaceutical sponsors generally have used parallel groups or crossover designs to compare active drugs with placebo or to compare 2 (or more) active drugs.[369] The primary end point is most commonly the maximum percentage decrease in FEV_1, especially for studies submitted to the US Food and Drug Administration (FDA)[369] in support of a bronchoprotective end point. Peak expiratory flow has also been used as an end point in some studies but not as a primary end point, and it is used less commonly than FEV_1.

In addition to the maximum absolute decrease in FEV_1, expressed as a percentage of baseline, the results may also be expressed as the $AUC^{0-60\ min}$ or until return to baseline and the time to recover to 95% baseline FEV_1 before and after therapy.[370] Baseline lung function may also be compared before and after therapy if a bronchodilator response is also being investigated.[6,24,29,112,369,371–374] Some studies have examined the percentage of individuals protected from EIB after therapy (responder analysis).

The maximum decrease in FEV_1 required to produce a positive test result varies with the situation in which the test is performed. In a clinical setting, the decrease in FEV_1 from baseline required to diagnose EIB is usually 10%[6] or perhaps 13%[37] or 15%.[40] As an inclusion criterion in a pharmaceutical trial, a 20% decrease in FEV_1 is usually required to define a positive challenge result (as described in FDA guidance).[369] In a clinical setting, it is desirable to produce as complete protection as possible so that there is no decrease in FEV_1 after exercise with treatment. In a pharmaceutical trial, protection may be defined as less than a 10% decrease in FEV_1 after exercise or 50% protection compared with placebo[375] for patients who are required to have a 20% decrease at the screening visit. When other end points are used (eg, AUC or time to recovery), the percentage of protection must also be adjusted for the situation in which the test is performed. Protection has been defined in some studies based only on statistically significant differences between responses after pretreatment with active drug compared with placebo. Attempts to define protection that have clinical relevancy have resulted in concepts such as "complete protection" and "clinical protection."[21,24] Complete protection may be suggested by predefined decreases of FEV_1 percentage within an accepted reference range (eg, $<$10% for FEV_1). Clinical protection has been defined as a 50% inhibition of the placebo response to exercise by drug pretreatment.[374,375] The 10% decrease is based on the mean plus 2 standard deviations of the decrease in healthy individuals,[38] and the 50% protection is based on the coefficient of variation for repeated tests.[375]

Numerous studies have been assessed in developing the evidence-based recommendations for therapy in this document, but there is little information on the consistency, presence, or absence of drug effect from recurrent testing in individuals. Also, most published evidence is from EIB studies in patients with clinically diagnosed (and usually atopic) asthma, and recommendations made herein are based on these data.[2,7,204] Information suggesting possible differences in pathogenesis of EIB and response to pharmacotherapies in apparently nonasthmatic elite athletes is summarized elsewhere in separate sections ("Pathophysiology of Exercise-Induced Bronchoconstriction" and "Competitive and Elite Athletes"). It is recommended that this

section on therapy be used largely as a starting point on which to base a trial of best therapy for a patient with EIB tempered by the responsiveness and needs of that individual patient over time. Failure to demonstrate inhibition or significant attenuation of apparent EIB by effective bronchoprotective agents should indicate the need for reevaluation of the diagnosis.

β_2-Adrenergic Receptor Agonists

Summary Statement 38. Inhaled β_2-adrenergic receptor agonists are the most effective group of agents for short-term protection against EIB and for accelerating recovery of FEV_1 to baseline when given after a decrease in FEV_1 after exercise. A

β_2-Adrenergic receptor agonists are the single most effective therapeutic group of agents for acute prevention of intermittent EIB.[29,271,372–380] They attenuate or protect against EIB in most patients.[13,29,271,376,378,381] Their effectiveness may relate in large part to their action as functional agonists acting directly on BSM receptors and probably by inhibiting mast cell mediator release.[123,382,383] These agents also are the most effective group of agents for enhancing recovery of FEV_1 to baseline values when given after a decrease after exercise.[371,372]

Summary Statement 39. When given as a single dose or on an intermittent basis, SABAs and LABAs may protect against or attenuate EIB; SABAs are usually effective for 2 to 4 hours and LABAs for up to 12 hours. A

Early investigations of β_2-adrenergic drugs developed for asthma showed that these agents were highly effective in protecting against EIB when inhaled 5 to 20 minutes before exercise.[373,376–378] Protection was found to last from 2 to 4 hours after inhalation, with most studies showing a duration at the lower end of this interval.[384–386] There appear to be no substantial differences among SABAs currently in use.[386–388] Mast cell stabilizers, described below, have been used as add-on therapy to supplement SABAs in increasing the degree of bronchoprotection.[29,380]

Two LABAs are currently in use and differ in their actions, mainly in their onsets of effect. Formoterol has a more rapid onset of bronchodilator and bronchoprotective action; in contrast, salmeterol requires 15 to 30 minutes.[389,390]

Summary Statement 40. Daily use of β_2-adrenergic agents alone or in combination with ICS usually will lead to tolerance manifested as a reduction in duration and/or magnitude of protection against EIB and a prolongation of recovery in response to SABA after exercise. Therefore, monotherapy with adrenergic agents is generally recommended for use only on an intermittent basis for prevention of EIB. A

Prolonged duration of a bronchoprotective effect, for as long as 12 hours, has been shown for these drugs after the first dose in β_2-agonist–naive patients.[385,391–396] However, many patients are not protected for this entire dosing interval, and the optimal dosing interval for bronchoprotection for EIB may be closer to 6 hours on average.[385,392,393,395] Prolonged protection with intermittent use of LABAs is sustained,[392,395–398] but daily maintenance use of LABAs (and SABAs) often results in some loss of bronchoprotection ("tolerance") with cross-tolerance to other β_2-agonists.[25–27,393,399–402] Moreover, daily use of LABAs and SABAs may actually increase the severity of EIB.[401,402] Of additional concern, the degree of tolerance may increase with increasing bronchoconstriction, potentially putting patients in severe asthma attacks at risk of less bronchodilator responsiveness at the time of greatest need.[403] Therefore, only intermittent use of adrenergic agonists is recommended for bronchoprotection. Although some individuals may have a greater propensity than others to develop tolerance, only a small number of patients are required to demonstrate tolerance,[27,401–406] suggesting that tolerance occurs in most patients. Tolerance occurs even when patients are also receiving ICS.[26,28]

The onset of tolerance can be rapid. By extrapolation of the effects on methacholine-induced bronchoconstriction[27] and other challenges such as AMP,[407] it may occur within 12 to 24 hours after a first dose.[27,407–409] The degree appears to increase with constant β_2-agonist use before it reaches a plateau.[27] By similar extrapolation, sensitivity to β_2-agonists may recover within 72 hours after the last dose of β_2-agonist use.[27]

Summary Statement 41. Regular (ie, daily) use of β_2-agonists for EIB leads to relative loss of efficacy of the agent. A

Tolerance may not develop when β-agonist use is limited to an interval of 48 to 72 hours.[410] However, a longer period for recovery may be required for other stimuli such as allergen challenges.[411] Tolerance is manifested most strikingly by a decrease in effectiveness of SABA[412] and by a shortening of duration of LABA effect,[26,28,391,393,396] in 1 study to less than 3 hours,[413] and by prolongation of recovery from bronchoconstriction.[27,401] The presence of tolerance is often missed clinically because a patient is rarely challenged at the point of care; consequently, the shorter duration of protection and the prolonged recovery time are not revealed. Importantly, prescribing additional doses of adrenergic aerosol immediately before exercise may unintentionally contribute to further generation of tolerance.

The mechanism(s) by which long-term (daily) use of β_2-agonists lead to tolerance is unclear. A number of observations have led to suggestions for possible mechanisms involved in the development of "tolerance." Long-term exposure of β-receptors to β_2-agonists results in uncoupling and internalization or sequestration in the cells where they are degraded.[414] This net loss in the number of available functional β-receptors[415] results in "downregulation" of responsiveness to β_2-agonists, which manifests as a lack of clinical protection to bronchoconstrictive stimuli. Restoration of sensitivity requires resynthesis of the receptor to the active state. This resynthesis is observed clinically within 72 hours of cessation of exposure to β_2-agonist.[27,410]

Stimulation of mast cell β-receptors normally inhibits mediator release. The process of β-receptor desensitization varies markedly among different cell types; bronchial mast cells are more easily desensitized than are BSM cells.[414,416] Downregulation appears to occur more readily in mast cells as may occur with therapeutic administration of β_2-agonists. For this

reason, the clinical effects of downregulation are evident more rapidly on mast cells with an effect on bronchoprotection than on smooth muscle and bronchodilation.[417] The downregulation of mast cell β-receptors not only enhances mediator release but potentially enhances bronchoconstriction as well.[192,193,383,401,418]

This downregulation or tolerance is demonstrated clinically as a reduction in duration of β_2-agonist bronchoprotection to stimuli such as exercise, which depends on mast cell mediator release for bronchoconstriction. Tolerance to bronchodilation is demonstrated by prolongation of the time of recovery from bronchoconstriction in response to usual doses of β_2-agonists.[27,401,402,419]

Downregulation of the β_2-receptor is accompanied by augmentation of pathways mediated through the LT, histamine, and thromboxane receptors. Activation of these receptors has the added potential to enhance bronchoconstriction.[194,195,382,401,402,420] Also, BHR may be induced by non–mast cell mediator mechanisms involving cholinergic agonists, for example, independently or with mast cell mediator mechanisms.[421–423]

The complexity of mechanisms involved in β-adrenoreceptor functioning, however, is emphasized in a review.[424] In investigations primarily using a mouse model, long-term β_2-agonist exposure caused an increase, rather than decrease, in contractile signaling. Unexpectedly, long-term exposure to a highly selective β-receptor antagonist (ie, β-blocker) resulted in upregulation of β_2-adrenoreceptors and bronchoprotection.[425] An open-label investigation in humans with chronic mild asthma reported results consistent with this latter finding in the mouse model.[425] Consequently, it is clear that a better appreciation of the mechanisms of β-adrenoreceptor functioning is needed. A more thorough understanding of the difference between the effects of intermittent and long-term use of β_2-adrenergic agonists, BHR, and the production of tolerance is necessary.

From a clinical point of view, potential concerns associated with tolerance with long-term use of SABAs or LABAs need to be recognized. Intermittent use of β_2-agonists is preferred and recommended for bronchoprotection.

The use of LABAs as daily monotherapy to provide overall asthma control is not recommended.[33] When ICS alone are not adequate in controlling chronic asthma, LABAs are often combined with ICS to provide effective maintenance therapy; however, there is no convincing clinical evidence that this combination diminishes tolerance to the bronchoprotective effect of LABAs in asthma or EIB with asthma.[26,28,426] Long-acting β2-agonists alone used intermittently, up to 3 times a week, do not appear to be associated with tolerance and may be prescribed for EIB.[410,427]

LT Inhibitors

Summary Statement 42. Daily therapy with LT inhibitors does not lead to tolerance and can be used for intermittent or maintenance prophylaxis; however, it provides protection that may not be complete and has no use to reverse airway obstruction when it occurs. A

The role of LTs in EIB is to sustain the bronchoconstrictive and inflammatory response, although their role appears to vary significantly among patients. Correspondingly, inhibitors of the LT pathway (LTRAs and lipoxygenase inhibitors) are effective in enhancing recovery, and again, there is much variability in their effectiveness, completely blocking EIB in some asthmatic individuals but less so or not at all in others. There is a 30% to 80% attenuation of EIB, with approximately 50% of patients being responders. These percentages may vary, depending in part on the FEV_1 decrease required to make a diagnosis of EIB (>10%, >15%, or >20%) or used to define protection.[24,379,400,428] Most patients do not experience complete protection.[24] This is not surprising given that other mediators (eg, PGD_2 and histamine)[116,429] are involved in EIB.

Various LTRAs have been found to be effective in attenuating EIB.[430,431] Most studies have examined specific LTD_4 receptor antagonist, particularly montelukast. Montelukast is approved by the FDA for treatment of EIB in adolescents and adults. These LTD_4 antagonists are administered orally, although bronchoprotection has been reported when some inhibitors have been given by inhalation.[432–437] Montelukast acts within 1 to 2 hours of oral administration[112,434,437] and has a bronchoprotective activity for 24 hours.[112,124,370,438,439] Maximum protection may not be retained toward the end of this period.[440] Leukotriene receptor antagonists also accelerate the time to recovery from EIB.[124,412] Whereas LTRAs are not as effective overall in attenuating EIB as β_2-agonists,[24] tolerance does not develop with long-term use.[124,399,400,441] The variability in effect on EIB suggests populations of responders and nonresponders similar to that shown for the LT effects on overall asthma control.[138,442,443]

A second group of agents that affects the LT pathway by inhibiting synthesis are the lipoxygenase inhibitors. Lipoxygenase inhibitors have also been shown to attenuate EIB when given orally[428,436,444,445] or intravenously,[446] but the duration of inhibition of these compounds is relatively short[428,436] and they are not currently recommended for this indication.

Mast Cell Stabilizers

Summary Statement 43. Cromolyn sodium and nedocromil sodium (currently not available in the United States in an inhaled form) when inhaled shortly before exercise attenuate EIB but have a short duration of action. They do not have a bronchodilator activity. They may be effective alone or as added therapy with other drugs for EIB. A

Cromolyn sodium and nedocromil sodium are 2 structurally unrelated compounds that have no bronchodilator activity but have similar bronchoprotective activity against EIB when inhaled.[29,30,111] Several mechanisms have been proposed for these agents, including interference with mast cell mediator release of PGD_2.[123] The bronchoprotective effect is rapid[447] but of short duration (1–2 hours).[448,449] These agents

may be effective when taken alone or when inhaled shortly before, and perhaps simultaneously with, exercise and may increase overall inhibition of EIB when combined with other drugs used to diminish EIB.[29,377,448,450] Significant intersubject and between-study variability has been observed in the ability of these agents to attenuate EIB. Some studies found few or no subjects protected, whereas other studies showed complete protection.[108,451] Effectiveness of cromolyn may be dose related.[384,451,452] The formulations (1 mg per actuation) available in the United States did not deliver sufficient doses of cromolyn unless many inhalations were given (eg, as many as 20 at a time). Long-term use of either drug is not accompanied by tolerance. For this reason and because of their excellent safety profiles and rapidity of action, these agents can be used repeatedly to attenuate EIB in responsive individuals.[29,453]

Inhaled Corticosteroids

Summary Statement 44. Although ICS therapy can decrease the frequency and severity of EIB, its use does not necessarily eliminate the need for additional acute therapy with β_2-adrenergic agonists or other agents. A

Exercise-induced bronchoconstriction in otherwise symptomatic asthmatic patients is best controlled by maintenance anti-inflammatory treatment alone[9,41,42] or in combination with other short-term preventive treatment.[23,33,207] Inhaled corticosteroids improve overall asthma control in most patients with chronic persistent asthma. Use of ICS also is associated with attenuation of hyperresponsiveness to direct and indirect stimuli, including exercise.[13] The effect of ICS on asthma and EIB is dose[9,105] and time dependent and may be associated with decreases in inflammatory mediators.[32] The relationship between improvement in control of persistent asthma and bronchoprotection, however, is imperfect. Nevertheless, the degree of EIB is considered a reflection of asthma control (or lack of control), and moderate to severe EIB, in particular, strongly suggests need for reassessment of therapy or another diagnosis.

Some bronchoprotective effect with ICS has been recorded as early as 4 hours after the first dose.[32,106] After 1 week of long-term therapy, efficacy begins to plateau[9,103,105]; however, bronchoprotection may increase over weeks or even months until it reaches its final plateau.[8,41,454,455] Bronchoprotection has been shown to occur in 30% to 60% of asthmatic patients with EIB, with marked individual variability ranging from "complete" protection to little or no evidence of protection.[8] In the absence of definitive dose-ranging and repetitive studies in individual patients, it is not clear whether this reflects distinct subpopulations of responders and nonresponders (eg, a reflection of genetic differences).

Inhaled corticosteroids do not necessarily obviate the need for acute bronchoprotection for EIB. β_2-Adrenergic agonists can be added if necessary for short-term prevention of EIB.[371,372] When maintenance ICS are not sufficiently effective, LTRAs can be used to obtain added protection, while also administering β_2-agonists for acute bronchoprotection if necessary.[21,22,35,207]

Summary Statement 45. Inhaled corticosteroid therapy does not prevent the occurrence of tolerance from daily β_2-agonist use. A

The preponderance of evidence indicates little amelioration by ICS of tolerance to β_2-agonist bronchoprotection[26,28,412,426,456] and a shortened degree of bronchoprotection remains when ICS and LABAs are given together. Nevertheless, one study that assessed the combination of an ICS and LABA (fluticasone and salmeterol) for maintenance therapy in adult patients indicated better bronchoprotection at 1 and 8.5 hours after dosing compared with the same dose of fluticasone alone during 4 weeks. In that study, most patients receiving the combined therapy also exhibited greater complete (<10% decrease of FEV_1) protection and overall asthma control.[28] A somewhat similar study with the same agents in children and adolescents also indicated a small persistent effect of bronchoprotection when the combination was used compared with the ICS alone.[31]

Anticholinergic Agents

Summary Statement 46. Although ipratropium bromide has been inconsistent in attenuating EIB, a few patients may be responsive to this agent. A

Anticholinergic agents (atropine sulfate and ipratropium bromide) have bronchodilator activity[422] by blocking vagally mediated tone and have been used alone and in conjunction with SABAs with some success in treating acute exacerbations of asthma.[457] Efficacy of anticholinergic agents to prevent EIB,[458] however, has not been consistent in double-blind studies, especially in placebo-controlled trials.[459] Not all patients appear to respond to anticholinergic agents,[29,450,460,461] and responsiveness may be variable in the same patient.[462] Studies should be performed to determine the characteristics of the responder population (perhaps based on increased cholinergic contributions to EIB in some patients).[422]

Methylxanthines, Antihistamines, and Other Agents

Summary Statement 47. Drugs in several other pharmacotherapeutic classes, including theophylline, antihistamines, calcium channel blockers, α-adrenergic receptor antagonists, inhaled furosemide, heparin, and hyaluronic acid, have been examined for actions against EIB with inconsistent results. B

Theophylline and aminophylline are methylxanthines that have been used for long-term maintenance therapy to treat persistent asthma. In recent years these agents have only been used as adjunct therapy to ICS or similar maintenance therapy when further control of asthma is needed.[33,207] Caffeine also belongs to this class of drugs. Methylxanthines are nonselective phosphodiesterase inhibitors of the cyclic AMP and cyclic guanine monophosphate pathways that play a role in the pathophysiology of asthma. Methylxanthines are mild bronchodilators and modify EIB in some patients possibly in part due to their bronchodilator action.[463,464] There are studies,

Table 4. Bronchial Provocation Challenge Comparisons for EIB

	Methacholine bronchial provocation challenge	Histamine challenge	Laboratory-based exercise challenge	Sports-specific exercise challenge	Eucapnic voluntary hyperpnea	Hypertonic saline challenge	Inhaled powdered mannitol	Inhaled adenosine monophosphate
Direct (acts directly on tissue) vs indirect (mediator release) challenge	D	D	ID	ID	ID	ID	ID	ID
Sensitivity for diagnosing EIB	Fair	Fair	VG-E	VG-E	VG-E	Fair	Fair	Fair
Sensitivity for diagnosing asthma	VG	VG	Good	Good	Good	VG	VG	VG
Specificity for diagnosing EIB	Fair	Fair	E	E	E	VG	VG	VG
Specificity for diagnosing asthma	Good	Good	VG	VG	VG	VG	VG	VG
PPV for diagnosing EIB	Fair	Fair	VG	VG	VG	Fair-Good	Fair-Good	Good
Fair-Good PPV for diagnosing asthma	Fair	Fair	VG	VG	VG	VG	VG	VG
NPV for diagnosing EIB	Fair	Fair	VG	VG	VG	Fair	Fair	Fair
NPV for diagnosing asthma	VG	VG	Fair	Fair	Fair	Fair	Fair	Fair
Produces dose-response curve	Yes	Yes	No	No	No	Yes	Yes	Yes
FDA approved	Yes	No	N/A	N/A	N/A	N/A	Yes	No
Correlates with airway inflammation	Mi	Mi	H	H	H	H	H	H
Correlates with current EIB symptoms	Mi	Mi	Mi	Mi	Mi	Mi	Mi	Mi
Requires subjects to be capable of exertion (eg, relatively free of cardiac disease)	No	No	Yes	Yes	No	No	No	No
Causes severe decreases in FEV_1 (eg, greater than 30%)	No	No	Yes	Yes	Yes	No	No	No
Commonly causes cough	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Can perform sputum collection in conjunction with challenge	No	No	No	No	No	Yes	Yes	No
Provides response dose ratio	Yes	Yes	No	No	No	Yes	Yes	Yes

Abbreviations: D, direct; E, excellent; EIB, exercise-induced bronchoconstriction; F, fair; FDA, US Food and Drug Administration; FEV_1, forced expiratory volume in 1 second; F, frequently; G, good; H, high; ID, indirect; Mi, minimal; Mo, moderate; NPV, negative predictive value; PPV, positive predictive value; VG, very good.

however, that clearly show no benefit from methylxanthines given orally.[465] Methylxanthines exhibit a relatively narrow therapeutic index with potentially serious adverse events such as seizures. Selective phosphodiesterase inhibitors are safer and may have efficacy similar to the methylxanthines. One such agent, roflumilast, is a phosphodiesterase 4 inhibitor that has been reported to attenuate mild EIB.[466]

Some antihistamines have been reported to attenuate EIB[107,110,429,467–470] but with inconsistent results.[113,471] Other antihistamines appear ineffective.[472] A possible explanation for this variability may relate to differences in the intensity and duration of the exercise stimulus, with greater intensity required for participation of histamine in the pathogenesis of EIB.[125] Also, histamine is only 1 of the 3 main mediators that contribute to EIB. In addition, the antihistamine class has pharmacodynamic diversity. For example, antihistamines may inhibit mediator activation and release and act on end organs and other histamine receptors.[473] Different routes of administration and dosages of antihistamines may also be confounding factors in previous studies.[474]

Allergic rhinitis is a common finding in atopic asthmatic patients, and there is some evidence that effective treatment of nasal congestion and obstruction by nasal ICS is associated with at least mild reduction in EIB.[56,454] However, other evidence[472] suggests that antihistamines used in children with allergic rhinitis and EIB may not be bronchoprotective. The conclusion is that there is an absence of definitive studies that have determined effectiveness of nasal or systemic antihistamines, used to treat allergic rhinitis, for an effect on EIB. It is likely to remain common practice to use antihistamines to treat allergic rhinitis in the hope that there will be some effect on EIB. Definitive studies are still needed to confirm the utility of this practice.

Numerous other compounds have been examined for activity against EIB and may have moderate effectiveness in some situations.[378] These include calcium channel blockers,[475,476] inhaled furosemide,[477–479] some α-adrenergic receptor antagonists (oral and inhaled),[458,480] inhaled heparin,[481] and hyaluronic acid.[482] These agents do not always produce consistent results in preventing EIB. The effectiveness of some of these agents does not necessarily apply to other members of the same drug class, suggesting various mechanisms of action, not necessarily related to the obvious mechanisms attributed to each class of drug. The effectiveness of diverse kinds of drugs suggests that there are multiple mechanisms underlying EIB.[12] Although these drugs are not recommended for clinical use against EIB, these and other agents may be useful as probes in studying possible mechanisms underpinning EIB. In addition, it is important to recognize that these agents may interfere with clinical protocols that seek to examine the effects of other experimental drugs on EIB.

Nonpharmacologic Therapy

Summary Statement 48. Preexercise warm-up may be helpful in reducing the severity of EIB. A

Warm-up before exercise was studied on postexercise bronchoconstriction in athletes with EIB. Continuous warm-up before exercise was shown to cause significant decrease in postexercise bronchoconstriction in some athletes. This has importance in patient education, and health care professionals should tell patients that preexercise warm-up should be done at 60% to 80% HR_{max} to provide partial attenuation of EIB; this refractory period may last typically from 1 to 3 hours and occasionally 4 hours.[129–131] However, this does not alleviate the need for medications. Albuterol plus a warm-up gives better protection than the warm-up or albuterol alone.[483,484]

Summary Statement 49. Reduction of sodium intake and ingestion of fish oil and ascorbic acid supplementation may be helpful in reducing the severity of EIB. A

A low sodium diet maintained for 1 to 2 weeks decreases EIB, but long-term effects of a low sodium diet on either the prevalence or severity of asthma or on EIB are unknown. These studies involve small numbers of individuals and need to be replicated before a low-salt diet is widely recommended. The low-sodium diet may be considered in addition to pharmacologic therapy of EIB.[34,485,486]

There is some evidence that a variety of dietary factors, such as dietary ω-3 polyunsaturated fatty acids, can reduce EIB. If these data are reproducible, it may be a new and important therapy that is safe and effective.[34]

Two weeks of ascorbic acid supplementation has been shown to improve pulmonary function, asthma symptom scores, fraction of eNO, and urinary LTs in asthmatic patients with EIB. This provides a potential nonpharmacologic recommendation for EIB patients.[487]

Competitive and Elite Athletes

Summary Statement 50. Exercise-induced bronchoconstriction alone in elite athletes may have different characteristics than EIB with asthma in elite athletes or EIB in the general population. These divergent characteristics may include pathogenesis, presentation, diagnosis, management, and the requirement by governing bodies to obtain permission to receive pharmaceutical agents. D

Exercise-induced bronchoconstriction is common in elite athletes who do not otherwise have symptoms of asthma.

Summary Statement 51. Airway inflammation in elite athletes may be related to the high intensity of physical training, high minute ventilation, and inhalation of airborne pollutants and allergens. D

Exercise-induced bronchoconstriction in elite athletes may be associated with a mixed neutrophil-eosinophil type airway inflammation in contrast to the more commonly observed eosinophil-dominant inflammatory cascade reported with chronic asthma.[235] In addition, in elite athletes (especially those competing in high air pollution environments), Leukotrienes may play a predominant role in the EIB response.[166,189] Endurance athletes, in particular, may develop respiratory symptoms and have BHR as a consequence of prolonged strenuous exercise and training at high rates of ventilation. The underlying airway inflammation in elite athletes may also be related to the high

intensity of the physical training with high minute ventilation, which has potential to cause injury to the airway epithelium. This injury is likely to occur when exercise is performed in adverse environmental conditions, such as cold dry air, or when there is prolonged exposure to chemicals at indoor swimming pools or exhaust fumes from ice resurfacers used to groom ice hockey rinks.[158–160,162,163] The high minute ventilation may aggravate effects of environmental exposures during physical activity, permitting airborne allergens and irritants to enter the small airways. In the process of conditioning dry air in various sports activities, the airways may be injured, which is likely a consequence of the humidification process occurring deeper in the airways.[10,13]

Summary Statement 52. The diagnosis of EIB, whether alone or with asthma, in elite athletes may be difficult because history and presentation are not reliable. Objective testing is necessary to diagnose the condition accurately. A

Diagnosing EIB in elite athletes may be complicated by their apparently excellent physical condition, which causes the athlete and his or her supporting personnel (eg, coaches, family members, teammates, primary care physicians, and trainers) not to appreciate that he or she may be experiencing symptoms of asthma. Many elite athletes may not acknowledge or may even deny typical daily asthma symptoms, such as cough, wheezing, tight chest, or prolonged shortness of breath. Moreover, baseline pulmonary function tests may not indicate airway obstruction in these individuals. In fact, many athletes have higher than normal baseline pulmonary function such that a normal percentage predicted FEV_1 may be observed even in the presence of airway obstruction.

Various bronchial provocation challenges may be useful in identifying EIB. The indirect bronchial provocation challenges are most useful in this setting and include exercise challenge in the athlete's sport (either in the natural setting or simulated conditions in the laboratory), EVH, and inhaled hyperosmolar aerosols (mannitol, saline). The exercise challenge in the athlete's venue may be logistically difficult to accomplish; however, reproducibility of the response to a standardized exercise challenge in the laboratory can also be an issue.[488] Other tests, such as dry air laboratory exercise challenge, may be used as surrogates. In fact, because environmental and exercise intensity varies, a well-controlled dry air laboratory challenge may provide the most accurate and reliable test results. The challenge test recommended by the IOC-MC's Independent Panel on Asthma is EVH, and the same panel accepts mannitol testing.[35,99,292] Table 4 compares challenges, and descriptions of how these challenges should be performed and can be found in the "Diagnosis" section.

In a recent comparative study of Scottish elite swimmers, mannitol was associated with high baseline eNO and inflammatory phenotype, whereas field-based exercise and chlorine challenge identified swimmer-specific bronchoconstrictive response. Thus, chlorine exposure, which was associated with a sustained decrease in eNO, may represent a neurogenic response in these elite athletes.[489]

Summary Statement 53. In general, the treatment of EIB in patients who have asthma is similar in both recreational and elite athletes. However, the efficacy of therapy for EIB alone in athletes at any level is not well established. A

The management of EIB in elite athletes is similar to that for recreational athletes and should include reducing relevant environmental exposures as much as possible; treating associated comorbid conditions; appropriate pharmacotherapy for control of symptoms, prophylaxis, and rescue; and patient education.[35] An individualized exercise prescription considering the athlete's venue may need to be designed by the athlete and the specialist to provide adequate control of EIB or EIB with asthma (eg, swimmers).

Unfortunately, the environmental exposures are often not controllable because athletes may have to practice or compete for long periods in air that is cold, polluted, or has high pollen allergen or chemical irritant levels.

It is recommended that controller pharmacotherapy for athletes who have EIB with asthma should include daily ICS. The combination of ICS plus LABAs is not recommended because of the potential for tolerance to develop with daily use of β_2-agonists. This tolerance reduces the duration of bronchoprotection in exercise afforded by the β_2-agonist. In some patients with concomitant moderate to severe persistent asthma, however, combination therapy may have added utility. The athlete's performance results should be monitored carefully because spirometry and symptoms alone may not be reliable end points to monitor control of asthma. If symptoms of EIB in athletes who have asthma are not controlled despite appropriate inhaler technique and adherence with therapy, treatment can be stepped up by increasing the dose of ICS or addition of other medications. However, symptoms of EIB in the elite athlete who does not otherwise appear to have asthma have been reported to be less responsive to ICS, perhaps reflecting neutrophilic inflammation.[35,201] Consideration should be given to oral LT antagonists, inhaled cromolyn, and inhaled nedocromil.[30,109,114] There may be reason to believe that some individuals may respond better than others to any of these various agents, based on genetics or other differences.[490] Inhaled anticholinergics, such as ipratropium or tiotropium, may be considered, but studies on these drugs in asthma have given mixed results and they are not considered standard therapy for EIB.[35,491] Ideally, elite athletes should only use β_2-agonists intermittently due to the potential for tolerance described above.[35,99] A lack of appropriate response to therapy requires additional evaluation of the athlete and consideration of the differential diagnosis (see the "Differential Diagnosis" section).

Athletes in sports with high ventilation rates (eg, swimming, mountain biking, rowing, biathlon, cross country skiing, and skating events) may develop respiratory symptoms compatible with EIB alone, with or without demonstrating a positive challenge test result indicative of asthma. It has been proposed that the repetitive epithelial injury repair cycle, in response to high ventilation rate, results in changes in the contractile properties of BSM as a result of exposure to

plasma-derived products from exudation.[10] For some athletes who have allergy, this exposure may lead to in vivo passive sensitization of the BSM.[10] This epithelial injury and repair cycle[227,245] may represent a form of overuse syndrome, and therefore the athlete may benefit from limitation of activity; however, this may be unrealistic for the elite endurance athlete.[188] The pathogenesis of this type of BHR in athletes who only have EIB may be different from that classically observed in athletes who have chronic asthma, where inflammatory cells such as eosinophils are important. Thus, these athletes who have EIB alone may have different mechanisms for the cause of their symptoms and may not respond to the medications typically used for asthma.[492,493]

These parameters are also available on the Internet at http://www.jcaai.org.

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