

Challenges in the management of exercise-induced asthma

Expert Rev. Clin. Immunol. 5(3), 261–269 (2009)

William Storms

*The William Storms Allergy
Clinic, 1625 Medical Center
Point, Suite 190, Colorado
Springs, CO 80907, USA
Tel.: +1 719 955 6006
Fax: +1 719 955 9595
sneezedoc@stormsallergy.com*

Exercise and physical activity are common triggers of symptoms in patients with asthma, although some individuals – especially athletes – may have symptoms with exercise alone. Exercise-induced bronchospasm (EIB) describes airway hyper-reactivity that is observed following exercise in a patient who is not otherwise diagnosed with asthma; exercise-induced asthma (EIA) describes airway hyper-reactivity associated with exercise in a patient who has persistent asthma. Specific challenges affecting both the diagnosis and treatment of these conditions are discussed in this review. The past decade has seen substantial advances in our understanding of EIA and EIB, including new guidelines on their management. With appropriate therapy, all patients with exercise-related symptoms should be able to reach their desired level of performance.

KEYWORDS: β -agonist • airway hyper-reactivity • asthma • challenge test • controller therapy • exercise • exercise-induced asthma • exercise-induced bronchospasm • physical activity

Exercise and physical activity are common triggers of symptoms in patients with asthma, and the term exercise-induced asthma (EIA) has been used for almost 50 years to describe the characteristic bronchial hyper-reactivity (BHR) observed in response to exercise or physical activity [1]. EIA is not a unique form of asthma, nor is it a subtype or phenotype of the disease and, while more than 90% of asthma patients develop respiratory symptoms following an appropriate exercise challenge, others respond to normal activities of daily life with symptoms requiring treatment [1,2].

EIA or exercise-induced bronchospasm?

The EIA Work Group of the American Academy of Allergy, Asthma and Immunology has defined EIA as ‘the condition in which exercise induces symptoms of asthma in patients who have asthma’ [1]. Nonetheless, in many cases exercise is the primary – or only – apparent trigger of bronchospasm. While some investigators have labeled such cases as pure EIA [3,4], a better term might be exercise-induced bronchospasm (EIB). EIB describes airway hyper-reactivity that is observed following exercise in a patient who does not otherwise present with daily and chronic asthma symptoms and who is not diagnosed with asthma according to current asthma management guidelines (Box 1) [1–3]. In other words, these patients only have symptoms with exercise.

While patients with EIB do not have persistent asthma, they may have underlying airway

inflammation similar to that which exists in asthma; indeed, frequent exercise has been demonstrated to be associated with proinflammatory changes; thus, symptoms observed only in relation to exercise or physical activity indicate the potential for increased expression of airway hyper-reactivity and the possible need for daily maintenance therapy. These patients should be monitored on a regular basis [3].

The different terminology may contribute to differences in the reported prevalences of EIA. For example, the prevalence of EIA in patients with asthma is estimated to be 90%, while estimates of EIA in the general healthy population range from 5 to 20% [1]. Approximately 10% of otherwise healthy school children have been reported to have ‘EIA without other daily symptoms of asthma’ [5]. The reported prevalence of EIA in elite athletes ranges from 16 to 70% [1,3]. Many elite athletes only have symptoms with exercise, and the broad variation in prevalence rates probably reflects the association with specific sports and how the estimates were determined (e.g., an empiric trial of medication vs challenge tests). Athletes undertaking winter endurance sports have some of the highest incidences of reported EIB [1,3,6,7].

Pathophysiology of EIA & EIB

An underlying pathology of asthma is airway inflammation. While the mechanism is not completely understood, in the patient with

Box 1. Exercise-induced asthma or exercise-induced bronchospasm?

Exercise-induced bronchospasm is bronchospasm that occurs with exercise in a patient who has no evidence of asthma, based on current asthma management guidelines:

- Normal pulmonary function tests at rest
- No symptoms with normal activities of daily living
- No need to use β_2 -agonists (other than with exercise)
- Good Asthma Control Test score (or other questionnaire)

Exercise-induced asthma is bronchospasm that occurs in a patient who has documented persistent asthma, when they exercise

Data from [1–3].

EIA, the airway physiological response to exercise triggers or exacerbates the underlying inflammation of asthma [1,3].

Evidence indicates that alterations in airway humidity and temperature contribute to EIA. Vigorous physical activity is associated with increased inhalation by frequency and volume; the increased ventilatory rate results in evaporative changes affecting the respiratory mucosa. This airway drying leads to increases in the osmolarity of respiratory epithelial cells and subsequent inflammatory changes, including the activation of epithelial cells and airway mast cells, and the release of histamine, leukotrienes and other chemokines. Additionally, vascular dilation of small blood vessels involved in rewarming the airways following exercise may contribute to congestion and further release of inflammatory mediators [3,8]. In patients who have asthma, these changes in airway osmolarity and temperature are believed to trigger the characteristic symptoms of BHR. Increased levels of airway inflammatory cells and mediators have been observed in exercising athletes with and without BHR [9,10].

Exercise-induced changes in airway function are exacerbated in cold and/or dry air, possibly reflecting the involvement of additional physiologic pathways (e.g., cholinergic stimulation, pulmonary vasoconstriction and secondary reactive hyperemia) [4,8].

Box 2. Some atypical symptoms of exercise-induced asthma (and exercise-induced bronchospasm).

- Complaints of chest pain not associated with cardiac disease
- 'Locker room cough' or a dry cough lasting up to a day following exercise
- Difficulty sleeping related to nocturnal asthma symptoms that may be a manifestation of late-phase responses to exercise or physical activity
- Complaints of 'heavy legs' or 'feeling out of shape'
- Fatigue
- Abdominal pain
- Headaches or dizziness
- Muscle cramps
- Seasonal fluctuations of symptoms following exercise related to changes in humidity and levels of airborne allergens and pollutants
- Avoidance of activities, exercise and/or sports; children may not want to participate in 'sleepovers' or go to 'camp'
- Inability to keep up with peers
- Symptoms in children while playing (especially in relation to other triggers, such as animal dander, house dust mites, mold, tobacco and other smoke, and cold air)

Data from [1,3].

Challenges in diagnosing EIA & EIB

The differential diagnosis of EIA should include other respiratory or cardiac conditions that can cause exertional dyspnea, such as exercise-induced vocal-cord dysfunction, gastroesophageal reflux disease (GERD), exercise-induced hyperventilation, being 'out of shape' and exercise-induced anaphylaxis [1–3]. Patients with seasonal symptoms or whose symptoms worsen at certain times of the year should also be evaluated for

allergen sensitivities by skin-prick testing. In patients with chronic asthma, EIA may be a manifestation of poor asthma control, so overall control should be assessed along with an evaluation of comorbid conditions and how to optimize controller therapy [2].

Is it EIA or EIB?

All patients with suspected asthma (including suspected EIA) should be evaluated by their medical history and a physical examination, which should include examination of the ears, nose, throat and chest, and lung function tests performed before and after administration of a short-acting bronchodilator [2]. EIA is distinguished by asthma symptoms (e.g., cough, wheezing, chest tightness, shortness of breath and/or excess mucus) after exercising for 6–8 mins. Symptoms may or may not resolve in patients who continue to exercise [1,3]. Whenever possible, self-reported symptoms of EIA should be confirmed with a positive challenge test (see later) to avoid false-positive and false-negative diagnoses [1]. An algorithm for diagnosing suspected EIA and EIB is shown in FIGURE 1. The patient with EIB usually has normal pulmonary function tests (PFTs); whereas the patient with EIA usually presents with a less than normal forced expiratory volume in 1 s (FEV_1) and at least 12% reversibility following bronchodilator inhalation. Consultation with a respiratory specialist should be considered if the diagnosis is unclear.

For patients with asthma, the expression of EIA is affected by:

- The baseline level of asthma control (e.g., a patient with poorly controlled asthma might have symptoms from climbing the stairs at home);
- Comorbid conditions (e.g., rhinitis) that may alter the air-conditioning ability of the upper respiratory tract, thereby enhancing the likelihood of exercise-related symptoms;
- The specific characteristics of the sport or physical activity (e.g., cross-country skiing may produce symptoms at a lower threshold than running in warm air) [1,7].

The timing of symptoms is important but may vary. Recreational athletes and children playing hard or exercising during physical education class may complain of asthma symptoms that begin shortly (6–8 min) after strenuous activity. In other cases, particularly with prolonged

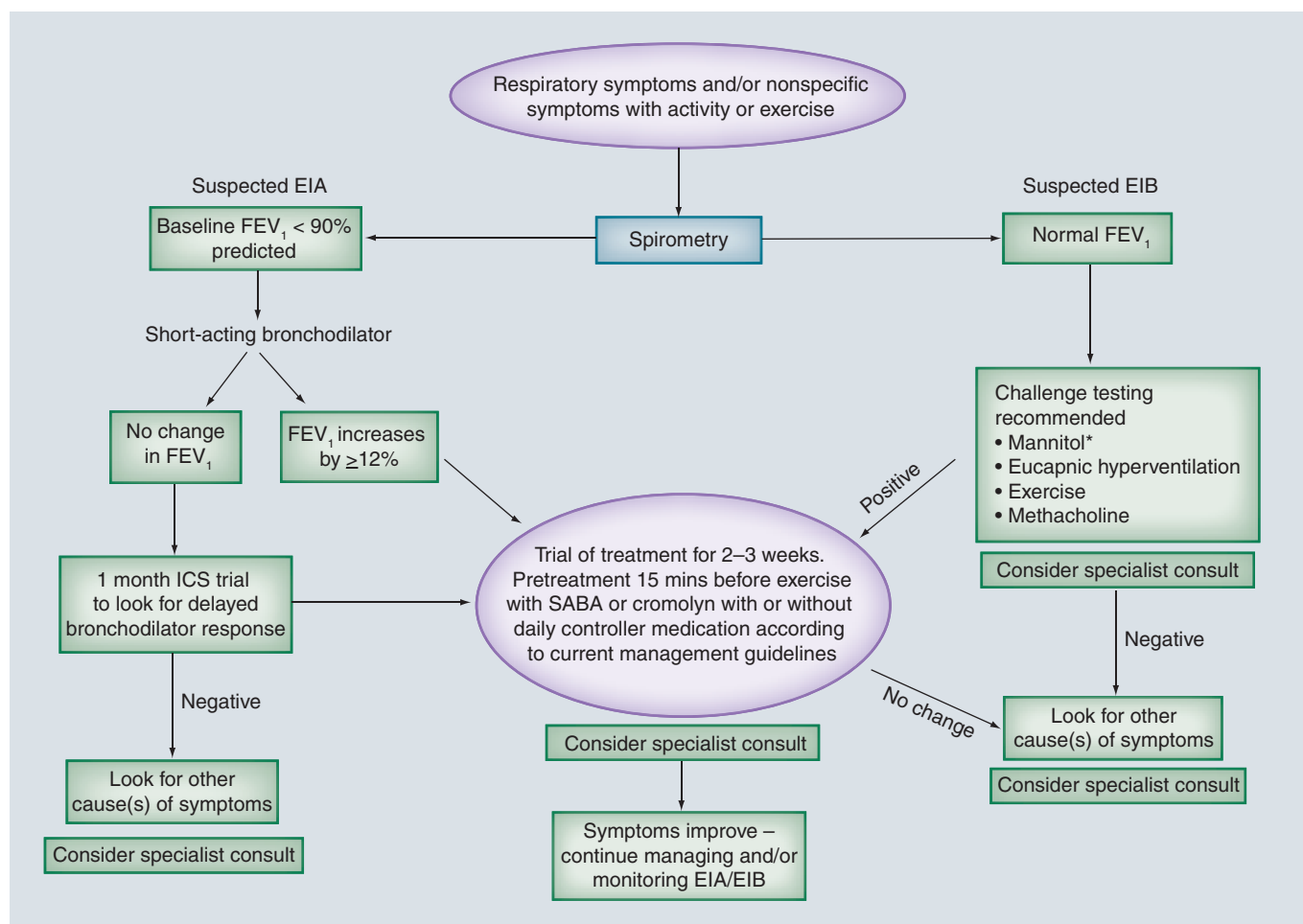


Figure 1. Algorithm for diagnosing suspected EIA and EIB in a patient who presents with respiratory symptoms and/or nonspecific symptoms with exercise and/or physical activity.

*Currently in review by the US FDA, although not yet approved.

EIA: Exercise-induced asthma; EIB: Exercise-induced bronchospasm; FEV₁: Forced expiratory volume in 1 s; ICS: Inhaled corticosteroid; SABA: Short-acting β_2 -agonist.

Adapted from [1–3,7].

activity, symptoms may not appear until after exercising [3]. Some patients describe ‘running through’ their asthma – in other words, they compensate by reducing the intensity of the activity until symptoms subside, after which they then increase the intensity of their exercise. These patients often have symptoms after stopping the activity [3].

Most patients recognize the association between their asthma symptoms and exercise or physical activity. School-age children need to be questioned about specific symptoms that occur in school – on the playground, in gym class and during any sports activities [2,3]. All patients with asthma should be asked about symptoms that occur or increase during intermittent sports activities (e.g., racquetball and tennis) and with activity in cold, dry air. Patients with both EIA and EIB, including competitive athletes, may present with nonspecific or atypical symptoms, such as poor performance or poor conditioning, ‘feeling out of shape’ and fatigue (Box 2) [3]. One of the most common nonspecific symptoms is a dry cough after exercising that can last for up to a day [3].

Which tests support the diagnosis?

Pulmonary function testing

Pulmonary function testing by spirometry at rest and postexercise should be used to confirm the diagnosis of EIA. Peak flow meters are not recommended owing to device variability, but may be useful for an individual patient to monitor his or her EIA once diagnosed [2].

As shown in Figure 1, patients with EIB have normal resting spirometry, with changes in pulmonary function (of $\geq 10\%$) evident after exercising; patients with EIA usually have abnormalities at rest as well as with exercise [7,11]. While an empiric trial of pre-exercise medication with an inhaled short-acting β_2 agonist (SABA) or cromolyn sodium is commonly used to confirm the diagnosis of EIA, it is not recommended nor supported by any data, and may result in an inaccurate or missed diagnosis.

Persistent asthma is usually indicated by reduced FEV₁ and/or at least 12% reversibility following inhalation of a short-acting bronchodilator [2]. For these patients, who have mild persistent

asthma and who have exercise-induced exacerbations of symptoms, a treatment trial that includes daily anti-inflammatory medication (inhaled steroid or montelukast) in addition to pre-exercise medication (as described previously) can help confirm the diagnosis. Follow-up is recommended after 3 weeks to allow the controller medication time to take effect [3].

For either empiric trial, further diagnostic evaluation is necessary if there is no obvious clinical improvement (FIGURE 1) [3].

Challenge tests

Exercise challenge

Exercise challenge is the most frequently used test, although it is not the preferred test by the International Olympic Committee (IOC) Medical Commission owing to its variability and lack of specificity. It is a direct way to confirm a diagnosis of EIA or EIB, and may be particularly useful when the clinic does not have the appropriate equipment for other types of challenge test [6,7].

The best type of exercise challenge is a sports-specific challenge or 'field test', with spirometry before and after exercise. This is often not possible, and testing for EIA usually involves standard treadmill, cycle ergometer, free-running, or step-testing in the office or in a pulmonary laboratory [1,3]. Schools often use free-running as a simple method of screening for asthma [1].

The intensity of the exercise is critical to performing an appropriate challenge test. According to the EIA Work Group, an exercise challenge should be of sufficient intensity to raise the patient's heart rate to 90% maximum for at least 2–4 min. A positive challenge is defined as one that produces at least a 10% reduction in FEV₁ from baseline values and symptoms that correlate with the drop in FEV₁ [1]. Ideally, temperature and humidity should be controlled; but this will not be possible for free-running or sports-specific challenges. High temperature and humidity may produce negative results. Under these conditions, if one test is negative, then a different challenge test should be carried out [3]. All challenge tests should include a flow/volume curve to evaluate for vocal cord dysfunction, which can mimic EIA.

Inhalation challenges

Indirect and direct inhalation challenges are also useful for confirming the diagnosis of EIA or EIB (TABLE 1). Direct challenges induce airway smooth muscle contraction but are not very specific; indirect challenges are more accurate, since they cause the release of endogenous mediators that subsequently result in bronchoconstriction [7,12,13]. The most common indirect challenges utilize

eucapnic voluntary hyperventilation (EVH; formerly referred to as isocapnic hyperventilation) or hyperosmolar aerosols; the IOC Medical Commission recommends either EVH or hyperosmolar challenge with mannitol dry powder to screen Olympic athletes [6]. Methacholine challenge is the most frequently used direct challenge test, but this is also the least specific test. Tests using other agents are available, but are not accepted by the IOC Medical Commission and will not be discussed here.

Eucapnic voluntary hyperventilation

Eucapnic voluntary hyperventilation uses hyperventilation as a trigger of EIA and correlates well with EIA in trained athletes [6,7,12–14]. The subject breathes rapidly (between 22 and 30 times FEV₁ in 1/min) for 6 min while breathing dry air with 5% CO₂ at between 20 and 25°C [6,7]. Although EVH is not difficult to set up, few respiratory physicians or pulmonary laboratories have the specialized equipment necessary to perform the test (FIGURE 2).

Mannitol

Mannitol powder delivered from capsules using a dry powder inhaler is an osmotic challenge test that can be used as a surrogate for exercise challenge and EVH in elite athletes. Spirometry is performed before and after mannitol inhalation, and the postchallenge cumulative reduction in FEV₁ correlates with the severity of the exercise-induced response [13]. Mannitol is currently used for EIA (and EIB) screening of athletes in Australia, Europe and Korea, but is not yet approved by the US FDA. This challenge has several advantages over other indirect and direct challenges: it is easy to administer, can be performed quickly and does not require specialized equipment [13,14]. When approved in the USA, it should become a commonly used test due to its simplicity, safety and established diagnostic value [1,6,14].

Hyperosmolar (4.5%) saline

Hyperosmolar (4.5%) saline aerosol inhalation can be used as a surrogate test for exercise challenge and EVH, simulating the effects of evaporative water loss on the airways. The hyperosmolar saline is delivered by a large-volume ultrasonic nebulizer, making this test less expensive and less complicated than EVH [14]. It has been shown to identify EIA in individuals with asthma, but with less accuracy than either EVH or mannitol [12,13].

Methacholine

Methacholine is the direct stimulus that is currently most often used to evaluate athletes because it is easily available in most pulmonary laboratories. It is not, however, a preferred test according to the IOC. Most guidelines recommend a provoking concentration to cause a 20% reduction in FEV₁ (PC₂₀) of less than or equal to 1 mg/ml to identify clinically recognized asthma [2]. However, methacholine responsiveness can vary depending on testing conditions, even in the same individual, and results are not always reflective of EIA [7,15].

Table 1. Challenge tests for exercise-induced asthma and exercise-induced bronchospasm.

Indirect	Direct
Adenosine monophosphate*	Carbachol*
Eucapnic voluntary hyperventilation	Histamine*
Mannitol†	Methacholine
Hypertonic saline	

*Not accepted by the International Olympic Committee Medical Commission.

†Currently in review by the US FDA, although not yet approved.

Data from [1,6,7,13].

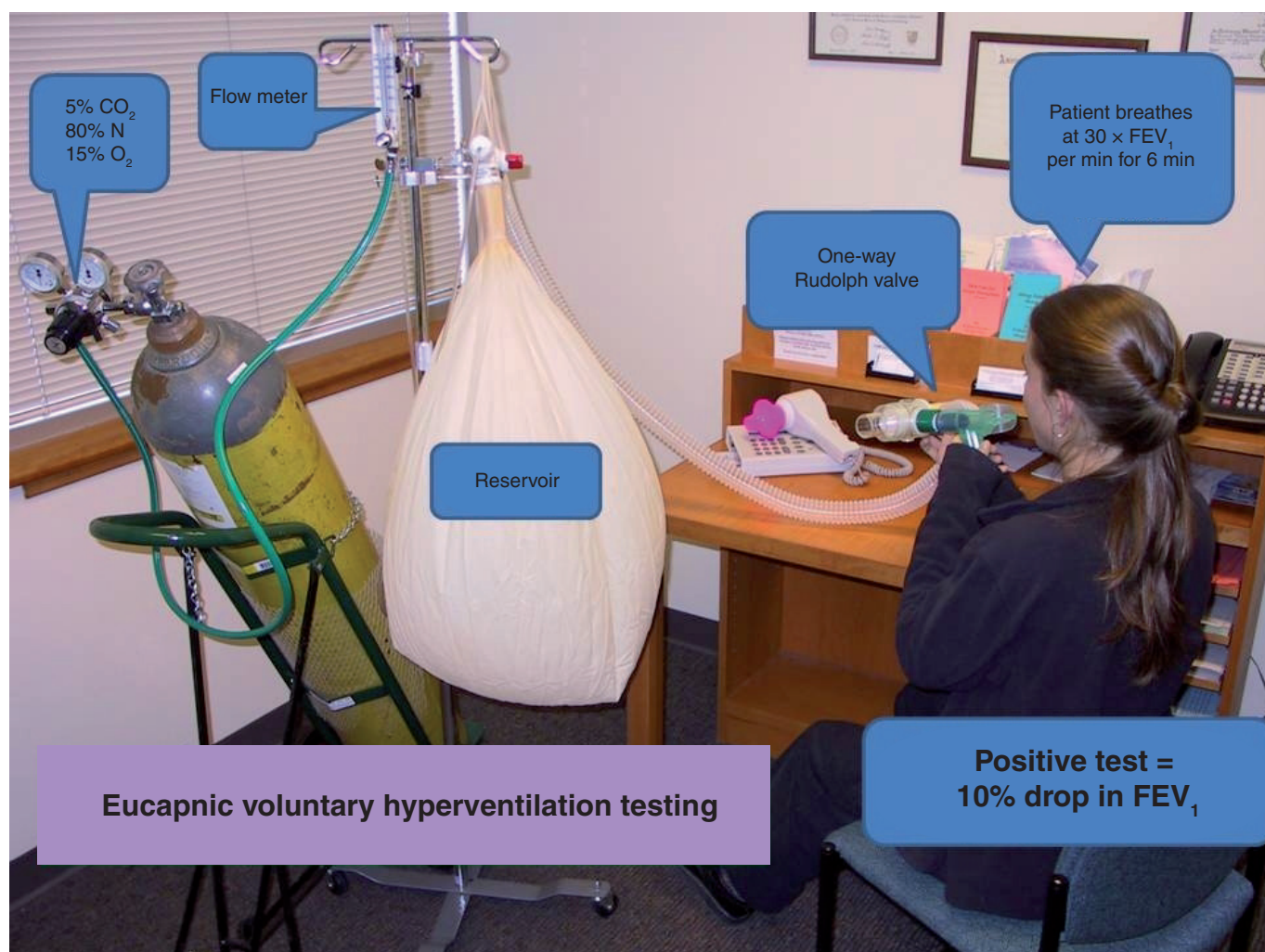


Figure 2. Specialized equipment necessary for performing eucapnic voluntary hyperventilation.

FEV₁: Forced expiratory volume in 1 s.

Photo courtesy of the author.

Exercise & the small airways

The role of the small airways in EIA and EIB is not well understood, but exercise may enhance the deep effects of exposure to allergens and irritants. Increased minute ventilation during physical activity pulls aeroallergens and pollutants deeper into the lungs. Indeed, some of the differences between the capacities of various sports to cause EIB may relate to environmental factors affecting the smaller airways, including exposure to seasonal and perennial allergens in sensitized individuals, cold or dry air and pollutants [6].

Challenges in treating EIA & EIB

As with asthma, treating EIA and EIB involves nonpharmacologic, pharmacologic and educational components.

Nonpharmacologic approaches

Warm-up

Exercise or physical activity is a trigger of asthma symptoms that cannot be avoided for most patients. However, an appropriate warm-up to 90% of the maximum heart rate prior to formal

exercise can reduce the severity of EIA and, in some cases, may completely mitigate EIA symptoms. This refractory period of protection can last for as long as 2 h, but the effect is not consistent between individuals, or for the same individual on different days. Thus, warming up should be used to reduce the risk of EIA symptoms, but should not be relied on as a primary means of EIA prophylaxis [3,6].

Environmental control

It is recommended that all asthma patients avoid their environmental triggers that might increase airway hyper-reactivity and, thereby, increase susceptibility to exercise-induced symptoms. However, this may not be possible for all patients. Some recommendations for recreational athletes and children at play include the following:

- For patients with seasonal allergies, exercise outdoors when allergens are at their lowest (i.e., in the early morning or evening) [2]. Allergic patients should always be treated for their allergies. If outdoor exercise must be conducted during a period of high

seasonal allergen counts (e.g., track meets in the autumn or spring), wearing a mask may be helpful. However, the use of a mask is not usually practical since many patients, particularly children, will not wear one;

- Avoid pollution, both outdoors and indoors. Air pollution can be subtle. Air quality data from the Environmental Protection Agency (EPA) confirms that students attending schools located near to industry and in areas of high exhaust from traffic may be exposed to toxic levels of air pollutants while on school property, including playing fields [101]. Asthmatic patients should be counseled to avoid exercising when air quality is impaired and/or under extreme conditions of temperature and humidity [6]. However, avoiding high levels of air pollution was not possible for many of the athletes competing in outdoor events at the 2008 summer Olympic games in Beijing, China; news reports showed some competitors wearing masks. Exposure to indoor air pollutants can be difficult to control, particularly for swimmers and ice skaters, as chemical fumes tend to accumulate just above the surface of the water or ice. For these individuals, appropriate warm-up and pharmacotherapy are essential [6]. If symptoms cannot be controlled, the individual should look for other ways to enjoy exercise;
- Avoid cold air. Appropriate warm-up and breathing through the nose to condition the cold air when exercising may be helpful. Wearing a mask or scarf over the nose and mouth may also help reduce the effects of cold air. However, individuals who remain sensitive to exercising in cold air despite warming up and appropriate pharmacotherapy should be advised to pursue other activities [1,6,16].

Pharmacologic therapy

Controller therapy

The most commonly used pharmacologic therapy for EIB is an inhaled SABA, which can be used to both prevent and treat symptoms. For some patients, a SABA taken 10–15 min prior to exercise may be all that is needed to control their EIB. However, current guidelines recommend that SABAs, while effective first-line therapy for exercise-induced symptoms, should not be used more than three times a week because of the tolerance that develops with constant β_2 -agonist use [1,3,16]. Most patients with EIA who exercise frequently should receive regular controller therapy for asthma (e.g., inhaled corticosteroids [ICS] or montelukast). Controller therapy should also be considered for patients who have EIB and who exercise regularly (i.e., daily – either year-round or in-season). These patients may have an underlying airway inflammatory condition, even without expressing other asthma symptoms, and should be treated according to the recommendations of current practice guidelines [1,3,16]. In this case, controller therapy is used to minimize – ideally to prevent – exercised-related symptoms, as opposed to controlling daily asthma symptoms [3]. These recommendations are in agreement with the January 2008 IOC Consensus Statement, which states that athletes who use β_2 -agonists (either SABAs or long-acting

β_2 -agonists [LABAs]) daily be told that ‘their effectiveness to prevent EIB will diminish over time’ and that ‘frequent use of β_2 -agonists may increase the bronchoconstrictor response to exercise and allergens’ [102].

The goal of controller therapy for all patients with exercise-induced symptoms is to reduce BHR and enhance disease control overall by treating the underlying airway inflammation, thereby permitting a greater level of physical activity. The preferred controller treatment is an ICS but other options (e.g., montelukast, cromolyn or nedocromil) may better meet the needs of some patients [1,2,16].

Through increased penetration and better distribution throughout the lungs, small-particle ICS formulations might provide added clinical benefit and address some of the subtle inflammatory changes associated with EIA and EIB. For example, because of a reduced particle size and reformulation into a solution, rather than a suspension, microfine hydrofluoroalkane beclomethasone dipropionate (HFA-BDP) shows comparable clinical efficacy to the older chlorofluorocarbon (CFC) formulation but at half the dose [17,18]. Approximately 55–60% of inhaled HFA-BDP reaches the lung and distributes diffusely, reaching both central and peripheral airways, compared with 4–7% of CFC-BDP, which deposits primarily in the central airway [18,19]. HFA-BDP has been suggested to reduce small-airway remodeling [20] and, as such, might have an impact on epithelial changes associated with the mechanical shear caused by high minute ventilation. More studies are warranted. Deposition of HFA-BDP is good even in patients with a poor inhaler technique [18], such as those who might use an inhaler ‘on the run.’

Pre-exercise medication

Pre-exercise medication usually involves treatment with an inhaled SABA 10–15 min prior to exercise. Another option is inhalation of the mast-cell stabilizer, cromolyn sodium, four to eight puffs 15 min prior to exercise. Cromolyn sodium can be used by itself or it may be added to a SABA in patients with more severe symptoms [2]. The leukotriene receptor antagonist, montelukast, an oral medication, may be helpful for some patients, particularly those who have difficulty using inhalers. For exercise, it should be taken once daily, at least 2 h prior to exercise [16,21]. Patients who are well controlled on their regular daily asthma medication may not always need pre-exercise therapy. For example, a well-controlled patient may be able to hike in warm weather, but might need premedication before exercising in cold, dry air. Nonetheless, no one can predict when symptoms will occur. As such, all patients with EIA or EIB should have a rescue inhaler easily available when exercising.

Albuterol metered dose inhalers (MDIs), propelled by CFCs, were phased out at the end of 2008 owing to their ozone-depleting chemistry. HFA-propelled MDIs are an ozone-friendly alternative with similar convenience and delivery systems. Albuterol HFA MDIs have been shown to deliver comparable doses to the lung and to have similar safety and efficacy profiles as the older CFC MDIs [22]. However, albuterol HFA MDIs may feel different on inhalation to some patients, owing to a more ‘mist-like’ spray. The new inhalers have been described as feeling ‘more gentle’ or

‘warmer’, probably related to a lower spray force than the CFC inhalers [23]. This may be preferred for some patients, as the gentler spray is less likely to cause coughing.

As noted above, daily use of SABAs (or LABAs) should be avoided owing to the possibility of tachyphylaxis and partial loss of the effectiveness of the β_2 -agonist over time. Tolerance can develop, even when β_2 -agonists are used in combination with an ICS [3,16]. Patients who exercise daily and need premedication may need to start or increase appropriate controller medication in order to minimize their usage of β_2 -agonists [16,24].

Treating breakthrough symptoms

β_2 -agonists also are the best studied and most commonly used medications for relieving breakthrough symptoms of EIA (and EIB), and current guidelines recommend that every asthma patient has a SABA inhaler for acute symptoms [2,16]. By using a SABA and reducing the intensity of their activity for a short period of time, the average noncompetitive athlete with EIB can usually continue to exercise even after experiencing breakthrough symptoms. Inhaled SABAs have an almost immediate onset of action that lasts up to 4 h. LABAs are not recommended for treating breakthrough symptoms [2,16].

For the patient with persistent asthma, breakthrough symptoms or poor endurance can be an indication of poor control and the need to increase daily controller therapy. Appropriate controller therapy should minimize the need for reliever medication [2,16]. Consultation with a respiratory specialist should be considered if the patient does not respond to treatment.

Monitoring EIA

Patients with EIA need to be monitored according to the guidelines for managing asthma, while those with EIB can be followed up, by phone or office visit, sooner, since the medications for EIB alone work quickly [2]. Follow-up should evaluate whether a step-up or step-down in therapy is needed, the patient’s technique for using his or her inhaler (as appropriate) and whether there are any comorbid conditions to be addressed. EIA symptoms may become more prevalent at certain times of the year – specifically, in the winter owing to cold air, during the patient’s allergy season, when humidity changes, during times of stagnant air and pollution, following a viral respiratory infection, or with allergic rhinitis. At these times, airway hyper-reactivity and the risk of breakthrough symptoms can increase and the patient may need to adjust his or her therapy. Treatment changes may be needed whenever the patient changes the intensity of their exercise. Temporarily limiting activity or changing sports or type of exercise can be considered as a last resort during times of severe symptoms; most patients should be able to exercise at their maximum level with proper treatment.

Patient education

Patient education for EIA should include discussion of which activities are most likely to cause symptoms and under what conditions, thereby increasing the patient’s awareness of his or her symptoms and how they respond to various environmental

triggers. Discussion of how or when to avoid environmental triggers is critical, and should include allergens, irritants and air pollution.

Information should also be provided on the role of pharmacotherapy, particularly controller medications, in treating EIA, and consideration of nonpharmacologic approaches to minimizing EIA symptoms. Discussion of nonpharmacologic approaches should include demonstration of appropriate warm-up techniques and, for some patients, discussion of nasal breathing to warm and humidify the inspired air. Patients should likewise be aware of any nasal symptoms or other comorbidities (e.g., GERD and upper respiratory infections) that may increase the severity of their EIA, and should learn how to treat them promptly and appropriately [1,3].

Patients should recognize that different levels of exercise and training require a step approach to managing EIA; medications need to be increased or decreased according to the intensity of the exercise. Just as training for a marathon differs from warming up for a five-mile jog, so too does managing EIA for these circumstances. Patients and physicians should know that even Olympic athletes who have asthma can compete, and that every patient should be able to perform at his or her desired level of activity with proper medical therapy.

What about the elite athlete?

Exercise-induced asthma is not uncommon in elite athletes who do not otherwise have asthma symptoms, and presentation, pathology and evaluation of elite athletes may be different from asthma patients who have symptoms with normal exercise [6,7].

Exercise-induced asthma in elite athletes may be associated with a mixed neutrophil–eosinophil-type airway inflammation versus the eosinophil-dominant inflammatory cascade reported with asthma and with EIA in recreational athletes. The underlying airway inflammation in elite athletes may be exacerbated by the high intensity of physical training and high minute ventilation, which can damage the bronchial epithelium [7]. The high minute ventilation may also aggravate the effects of environmental exposures during physical activity, permitting airborne allergens and irritants (e.g., chlorine derivatives in swimming pools, particulate matter from combustion as seen in the 2008 Summer Olympic Games and fumes related to machines used to groom ice rinks) to be drawn deeper into the lungs. Indeed, differences between the capacities of various sports to cause EIA may result in part from environmental irritants reaching the smaller airways, including exposure to seasonal and perennial allergens in sensitized individuals, as well as cold and dry air and pollutants [6,7].

Diagnosing EIA in elite athletes may be complicated by their seemingly excellent physical condition. Many elite athletes do not present with daily asthma symptoms, and baseline pulmonary function tests may not indicate EIA in these individuals. In fact, many athletes have ‘super-normal’ pulmonary function tests, which may be misleading. Challenge testing by EVH is recommended by the IOC Medical Commission, and it is now accepted that mannitol testing has comparable sensitivity to EVH [6,7,14].

The management of EIA 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, prophylaxis and rescue, and patient education [6]. Controller pharmacotherapy is recommended using ICS and, if EIA is not controlled despite appropriate technique and adherence to therapy, treatment can be stepped up by increasing the dose or by adding other medications [2,6]. However, asthma symptoms in elite athletes have been reported to be less responsive to ICS, perhaps reflecting the mixed airway inflammation [6].

Ideally, elite athletes should only use β -agonists infrequently owing to the potential for tolerance described previously [6,16]. A lack of appropriate response to therapy requires additional evaluation of the athlete.

Expert commentary

One of the most common triggers for patients with asthma is exercise or physical activity, and it is important for physicians to understand the best methods of diagnosing and treating EIA. However, transient EIB also may occur in isolation, without other regular symptoms of asthma. EIB is particularly prevalent in athletes, and its appropriate diagnosis and management is critical so that these individuals can participate in their chosen sports. The question of whether EIB is a distinct entity or whether it is a subtype of asthma has not been settled. However, the diagnosis and management of both EIA and EIB are similar. Symptom-based diagnoses should be confirmed by challenge testing, and treatment should include controller medication for most patients. Appropriate management should allow almost any patient to exercise at whatever level they desire.

Five-year view

It is this author's opinion that the next 5 years will see a substantial increase in awareness about EIA and EIB, not only among respiratory physicians and athletes, but also among primary care physicians and the general population of patients. The major

challenges to date have been appropriate diagnosis, particularly in elite athletes who otherwise may not have symptoms of asthma, followed by appropriate treatment – one that does not simply treat the symptoms, but also addresses the underlying pathology. The recommendation that patients who exercise regularly should use a daily controller medication is a significant step forward, and the number of athletes using controller medications (even if only during their athletic 'season') will undoubtedly grow with better understanding of tolerance to regular β_2 -agonist use and how controller therapy reduces airway hyper-reactivity and decreases the need for (and, therefore, potential tolerance to) β_2 -agonists.

This author also believes that we will see a better understanding of the impact of the exercise environment and air quality on lung symptoms, with recommendations for improving air quality being driven by athletes and associated organizations such as the IOC. Until then, we will probably see more athletes with EIA using air masks to filter, warm and humidify their inhaled air. Finally, FDA approval of the mannitol inhalation challenge test will be a big step forward for confirming the diagnosis of asthma and for screening athletes for EIA and EIB in the USA. The simplicity of the test and its documented safety and efficacy for diagnosing EIA (and EIB) will reduce errors of over- and under-diagnosis, thereby ensuring that patients get the treatment they need.

Acknowledgements

The technical expertise and editorial support of Judith Rosen Farrar, PhD, is gratefully acknowledged.

Financial & competing interests disclosure

Development of this manuscript was funded by unrestricted educational grants from Teva Pharmaceuticals, Ltd. and Pharmaxis, Inc. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Exercise-induced asthma (EIA) is a common problem affecting the general population of asthmatics, whereas the prevalence of exercise-induced bronchospasm (EIB) as a sole respiratory symptom in persons not otherwise diagnosed with asthma is reported to be high among some recreational and elite athletes.
- The diagnosis of EIA, and its differentiation from EIB, can be difficult due to reliance on symptoms for diagnosis. Confirmation of the diagnosis by an appropriate trial of medication and/or challenge test (the latter of which is preferred) is important.
- Respiratory symptoms indicative of EIB, such as breathlessness, cough, wheezing and chest tightness, which occur regularly upon exercising, are suggestive of asthma and should be regarded as a 'red flag.' Patients presenting with these symptoms should be carefully monitored for additional signs of underlying airway inflammation.
- Inhaled mannitol is a simple indirect challenge test that is under review by the US FDA. It does not require specialized equipment, can be performed quickly and safely and, when approved, should become a commonly used test to confirm the diagnosis of asthma and to screen athletes for EIA and EIB.
- Short-acting β_2 -agonists are the most commonly used medications to treat EIA and EIB; however, a daily controller medication is recommended for all patients with persistent symptoms and to reduce the need for (and tolerance to) bronchodilators.
- The role of the small airways in EIA is a topic of current debate; however, medications that reach the peripheral airways may reduce damage associated with mechanical shear related to high minute ventilation.
- All patients with EIA and EIB should recognize and understand what causes their symptoms and what makes their symptoms worse. In addition to treating their condition with medications, patients should be informed about nonpharmacological methods to reduce their symptoms.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

- 1 Weiler JM, Bonini S, Coifman R *et al.* American Academy of Allergy, Asthma and Immunology Work Group Report: exercise-induced asthma. *J. Allergy Clin. Immunol.* 119, 1349–1358 (2007).
- **The report of the American Academy of Allergy, Asthma and Immunology Work Group makes recommendations for current approaches to managing exercise-induced asthma (EIA) and identifies remaining controversial issues.**
- 2 National Asthma Education and Prevention Program. Expert Panel Report 3. Guidelines for the diagnosis and management of asthma. The National Heart, Lung, and Blood Institute; US Department of Health and Human Services, National Institutes of Health. NIH Publication No. 07–4051 (2007).
- 3 Storms WW. Asthma associated with exercise. *Immunol. Allergy Clin. N. Am.* 25, 31–43 (2005).
- 4 Helenius I, Lumme A, Haahtela T. Asthma, airway inflammation and treatment in elite athletes. *Sports Med.* 35, 565–574 (2005).
- 5 Hallstrand TS, Curtis JR, Koepsell TD *et al.* Effectiveness of screening examinations to detect unrecognized exercise-induced bronchoconstriction. *J. Pediatr.* 141, 343–349 (2002).
- 6 Fitch KD, Sue-Chu M, Anderson SD *et al.* Asthma and the elite athlete: summary of the International Olympic Committee's Consensus Conference, Lausanne, Switzerland, 22–24 January 2008. *J. Allergy Clin. Immunol.* 122, 254–260 (2008).
- **Excellent discussion of issues associated with diagnosing and managing the athlete with EIA/exercise-induced bronchospasm (EIB) from the perspective of the International Olympic Committee.**
- 7 Carlsen KH, Anderson SD, Bjermer L *et al.* Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms, and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EACCI) in cooperation with GA²LEN. *Allergy* 63, 387–403 (2008).
- **First part of the latest European recommendations on EIA. Discussion is in depth and current.**
- 8 McFadden ER Jr, Nelson JA, Skowronski ME, Lenner KA. Thermally induced asthma and airway drying. *Am. J. Respir. Crit. Care Med.* 160, 221–226 (1999).
- 9 Sue-Chu M, Larsson L, Moen T, Rennart SI, Bjermer L. Bronchoscopy and bronchoalveolar lavage findings in cross-country skiers with and without 'ski asthma.' *Eur. Respir. J.* 13, 626–632 (1999).
- 10 Verges S, Devouassoux G, Flore P *et al.* Bronchial hyperresponsiveness, airway inflammation, and airflow limitation in endurance athletes. *Chest* 127, 1935–1941 (2005).
- 11 Crapo RO, Casaburi R, Coates AL *et al.* Guidelines for methacholine and exercise challenge testing – 1999. *Am. J. Respir. Crit. Care Med.* 161, 309–329 (2000).
- 12 Anderson SD, Brannan JD. Methods for 'indirect' challenge tests including exercise, eucapnic voluntary hyperpnea, and hypertonic aerosols. *Clin. Rev. Allergy Immunol.* 24, 27–54 (2003).
- 13 Rundell KW, Slee JB. Exercise and other indirect challenges to demonstrate asthma or exercise-induced bronchoconstriction in athletes. *J. Allergy Clin. Immunol.* 122, 238–246 (2008).
- **Excellent overview of current methods of challenge testing for athletes with EIA or EIB.**
- 14 Holzer K, Anderson SD, Chan HK, Douglass J. Mannitol as a challenge test to identify exercise-induced bronchoconstriction in elite athletes. *Am. J. Respir. Crit. Care Med.* 167, 534–537 (2003).
- 15 Kotaru C, Coreno A, Skowronski M, Muswick G, Gilkeson RC, McFadden ER Jr. Morphometric changes after thermal and methacholine bronchoprovocations. *J. Appl. Physiol.* 98, 1028–1036 (2005).
- 16 Carlsen KH, Anderson SD, Bjermer L *et al.* Exercise-induced asthma, respiratory and allergic disorders in sports and the relationship to doping: part II of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EACCI) in cooperation with GA²LEN. *Allergy* 63, 492–505 (2008).
- **Second part of the latest European recommendations on EIA. Discussion is in depth and current.**
- 17 Lipworth BJ. Targets for inhaled treatment. *Respir. Med.* 94(Suppl.), S13–S16 (2000).
- 18 Colice GL. New developments in inhaled corticosteroids. *Allergy Asthma Proc.* 27, 332–340 (2006).
- 19 Holz O, Zuhlke I, Einhaus M *et al.* Direct measurement of BDP and 17-BMP in bronchial and peripheral lung tissue after inhalation of HFA- vs CFC-driven aerosols. *Pulm. Pharmacol. Ther.* 17, 233–238 (2004).
- 20 Bergeron C, Hauber HP, Gotfried M *et al.* Evidence of remodeling in peripheral airways of patients with mild to moderate asthma: effect of hydrofluoroalkane-flunisolide. *J. Allergy Clin. Immunol.* 116, 983–989 (2005).
- 21 Singulair® (montelukast sodium). Package insert. Merck and Co., Inc. (2008).
- 22 Lumry W, Noveck R, Weinstein S *et al.* Switching from ventolin CFC to ventolin HFA is well tolerated and effective in patients with asthma. *Ann. Allergy Asthma Immunol.* 86, 297–303 (2001).
- 23 Boccuzzi SJ, Wogen J, Roehm JB. Use of hydrofluoroalkane propellant delivery system for inhaled albuterol in patients receiving asthma medications. *Clin. Therap.* 22, 237–247 (2000).
- 24 Hancoux RJ, Subbarao P, Kamada D, Watson RM, Hargreave FE, Inman MD. B₂-agonist tolerance and exercise-induced bronchospasm. *Am. J. Respir. Crit. Care Med.* 165, 1068–1070 (2002).

Websites

- 101 USA Today Special Report. The Smokestack Effect: Toxic Air and American Schools
<http://content.usatoday.com/news/nation/environment/smokestack/index> (Accessed 5 March 2009)
- 102 Ljungqvist A, Fitch KD, Sue-Chu M, *et al.* International Olympic Committee Consensus Statement on asthma in elite athletes
http://multimedia.olympic.org/pdf/en_report_1301.pdf (Accessed 5 March 2009)

Affiliation

- William Storms, MD
The William Storms Allergy Clinic,
1625 Medical Center Point, Suite 190,
Colorado Springs, CO 80907, USA
Tel.: +1 719 955 6006
Fax: +1 719 955 9595
sneezedoc@stormallergy.com

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.