Exercise-Induced Bronchoconstriction

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ABSTRACT

Exercise-induced bronchoconstriction (EIB) refers to acute airway narrowing after whole-body exercise in persons with or without diagnosed asthma. This review provides a broad overview of EIB, including its definition, pathogenesis, physiological and clinical characteristics, prevalence, procedures for proper diagnosis and consideration of differential diagnoses, and discussion of pharmacologic and nonpharmacologic therapy. *Journal of Clinical Exercise Physiology.* 2016;5(3):37–47.

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Bronchial asthma is characterized by the variable presence of 3 interrelated characteristics, namely, airway inflammation, airways hyperresponsiveness (AHR), and a variable and reversible airway obstruction (1). In all cases of asthma, the airways are hypersensitive and narrow excessively in response to a variety of stimuli. Such stimuli include inhaled antigens (e.g., ragweed, dust mite and cockroach excrement, animal dander, mold), airborne chemicals (e.g., tobacco smoke, particulate matter, chlorine derivatives), chemicals in foods (e.g., peanuts), and cold and dry air (1). Whole-body exercise, in particular, is a potent trigger of airway narrowing in the majority of patients with asthma, a phenomenon known as exercise-induced asthma.

Whole-body exercise may also cause airway narrowing in persons who do not meet general diagnostic criteria for bronchial asthma (2–4). Such individuals exhibiting bronchoconstriction following exercise, but with the apparent absence of classic asthma, are said to have exercise-induced bronchoconstriction (EIB) rather than exercise-induced asthma. However, asthma is a syndrome that actually consists of a variety of phenotypes with multiple combinations of pathologic alterations and physiologic manifestations (5,6); thus, diagnosis of asthma is not straightforward. Moreover, current recommendations for the general diagnostic approach and clinical management of airway narrowing following exercise do not consider whether the patient has been diagnosed with classic asthma (7). Thus, in this review we will use EIB to refer to airway narrowing following whole-body exercise in any person, irrespective of his or her clinical status.

DEFINITION OF EIB

Clinically, EIB is defined as a decrease in the forced expiratory volume in 1.0 second (FEV_1) following whole-body exercise. Generally, an FEV_1 decrease of 10% relative to baseline is considered significant airway narrowing (7). However, a more stringent cutoff that uses a 15% decrease in FEV_1 has also been recommended (8). There is no clear consensus on which cutoff is most appropriate. Among the general population, a 10% decrease in FEV_1 occurs at approximately 2 standard deviations from the mean response (9); this provides a sensible and relatively objective cutoff value. On the other hand, in subjects classified as nonasthmatic or asthmatic, there is wide variability in the pulmonary function response to exercise and considerable overlap exists between groups (10). Thus, a more stringent cutoff value will exclude a greater number of persons testing positive for EIB; the higher cutoff will increase specificity of diagnosis and minimize false-positives due to such factors as poorly performed forced exhalations, cough, or calibration drift, for example.

Importantly, EIB is defined as a postexercise reduction in pulmonary function relative to baseline. The maximum bronchoconstriction occurs between 10 and 15 min after exercise, and thereafter resolves spontaneously so that airway function is largely recovered within 60 min. Based on the percent decrease in FEV_1 following exercise, the severity

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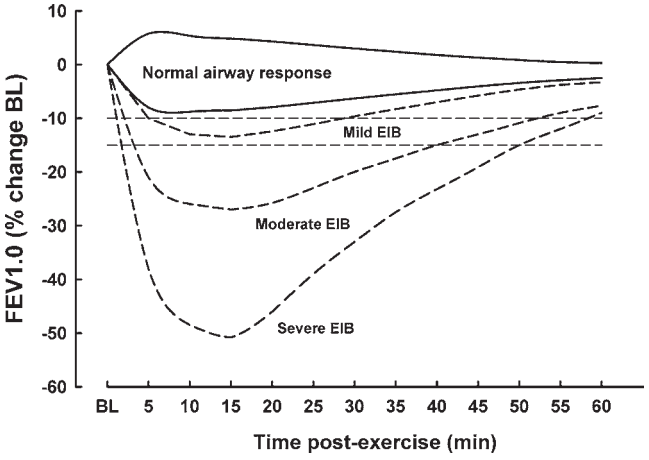
FIGURE 1. Range of normal airway response to exercise and range of severity for exercise-induced bronchoconstriction (EIB). In persons without EIB (normal airway response), whole-body exercise was followed by either bronchodilation or a minor bronchoconstriction that resolved within 20–30 min after exercise. Clinically significant EIB was defined as a decrease ≥10% in forced expiratory volume in 1 second (FEV_1) after exercise; a more stringent definition requires a decrease ≥15% in FEV_1 after exercise (horizontal dashed lines). The severity of EIB was classified as mild, moderate, or severe depending on the decrease in FEV_1 after exercise (see text for details). In most cases, the postexercise airway narrowing spontaneously resolved within approximately 60 min after exercise cessation. BL indicates baseline.



of EIB is categorized as mild (≥10% and <25%), moderate (≥25% and <50%), or severe (≥ 50%) (7). Figure 1 depicts these general characteristics of EIB. Figure 2 shows individual pre- and postexercise maximal flow-volume curves and time-volume traces for a subject with EIB.

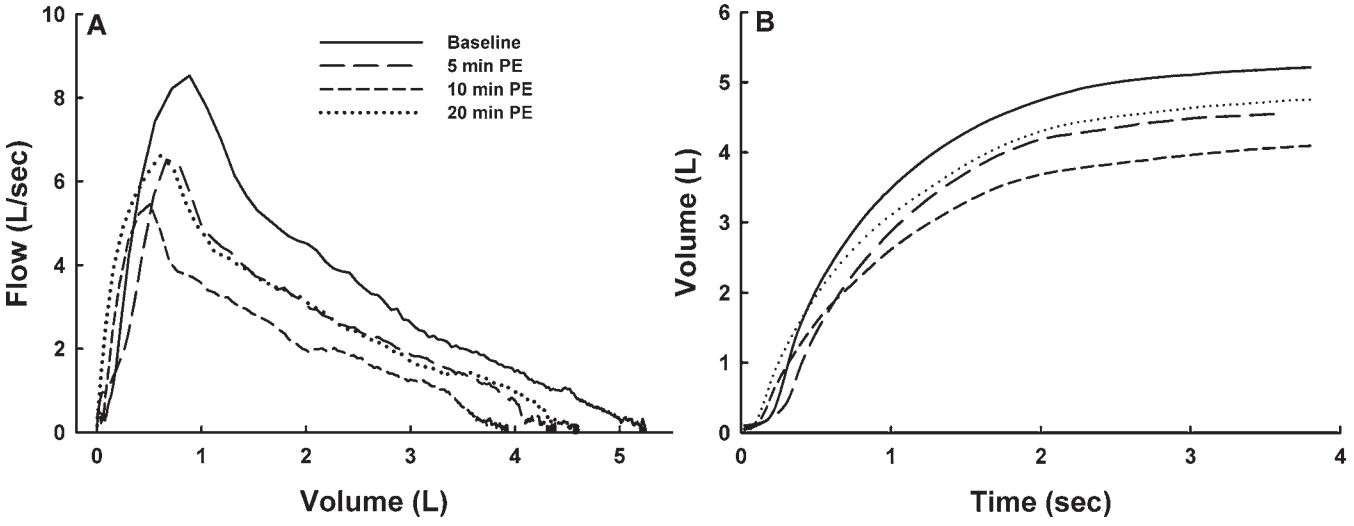
CLINICAL MANIFESTATIONS

The airway narrowing after exercise causes shortness of breath, difficulty breathing, chest tightness, wheeze. and cough. Importantly, these well-known clinical symptoms demonstrate significant between-subject variability. Patients will vary widely in both their predominant symptom(s) and the intensity of the symptom(s) experienced. Indeed, previous studies have shown substantial discordance between perceived symptoms and the extent of airway narrowing in persons with EIB (4,11–13). Thus, diagnosing EIB based on clinical symptoms alone is normally not recommended (14,15). In patients with symptoms following exercise who do not demonstrate decreased pulmonary function, alternative diagnoses should be considered (see the "Differential Diagnoses" section).

PREVALENCE

Determining the prevalence of EIB in asthmatic and nonasthmatic populations is challenging for several reasons. First, there is significant variability in the criteria used to define participants as asthmatic in studies of EIB prevalence. This is due in part to the fact that asthma not only encompasses a host of phenotypic manifestations but its presence has also been assessed by a variety of different measures. Unfortunately, many investigations use physician diagnosis of asthma or self-reported symptoms as the criterion for considering someone to be asthmatic. These cavalier inclusion criteria will result in an unknown percentage of participants who do not have active asthma. Conversely, investigations of EIB prevalence in the general population will include some participants with underlying asthma. Furthermore, both the outcome measure of airway narrowing (e.g., FEV_1 vs peak expiratory flow) and the threshold indicating significant airway narrowing (i.e., 10% vs 15% decrease in

FIGURE 2. (A) Maximal expired flow-volume curves at baseline and at 5, 10, and 20 min postexercise (PE) in a patient with asthma. Airflow was already substantially decreased at all lung volumes by 5 min PE and exhibited maximal reduction at 10 min PE. (B) Pre-exercise and PE time-volume traces in the same patient. Note the reduced airflow after exercise compared with baseline, which is indicative of airway narrowing and exercise-induced bronchoconstriction.



FEV_1) vary among studies. Finally, conditions of the inspirate are not normalized among studies; thus, in many cases the inspirate is either cooled or dried (or both), whereas ambient air is used in others. This is important, as the condition of the inspired gas has profound effects on the severity of EIB (16–18). Thus, EIB prevalence in different populations should be viewed as estimates based on an overall assessment of the literature while keeping in mind the variety of mitigating factors found in the studies.

The vast majority of persons with asthma are susceptible to EIB. However, the literature does report a variable prevalence between ~45% and 90% (19–21). In addition to the experimental and methodologic weaknesses in the literature discussed earlier, many factors interact to determine whether an individual with asthma demonstrates EIB on any given occasion. The severity of airway inflammation (which is always variable), current medication use, and conditions of the inspirate will all affect the airway response to exercise. It is likely that nearly all individuals with either persistent or fluctuating airway disease have the propensity for airway narrowing with exercise under the right conditions. It is important to understand that airway function and the degree of AHR vary on a daily, seasonal, and annual basis (21–23). Thus, a negative result for EIB does not unambiguously indicate that the patient does not have EIB; rather, it means the patient does not currently demonstrate AHR to exercise under the conditions of the protocol used.

In the general population, the change in pulmonary function after exercise follows a normal distribution (9). Moreover, studies in the general population have shown that FEV_1 is decreased by 10% to 20% following exercise or hyperpnea at 2 standard deviations from the population mean (9,24,25). The general population—which includes those with clinically relevant asthma— has a prevalence of EIB between approximately 7% and 20%, depending on the study (3,4,9,12,13,26). Among persons who do not have classic asthma, approximately 10% exhibit significant airway narrowing following exercise. It is not known whether this represents a subtype of the asthmatic syndrome or a discrete entity in and of itself.

In athletic populations, the prevalence of EIB is higher than in the general population. EIB prevalence in athletes ranges from approximately 10% to 60%, depending on the study (11,27–30). Investigations of EIB prevalence in athletes suffer from the same limitations as those in other populations; the actual prevalence of EIB in athletes resides somewhere within the range found in the literature. Activities requiring at least moderate increases in metabolic rate and ventilation are necessary to elicit EIB. Furthermore, athletes competing in sports requiring high ventilation rates in cold and dry air are the most likely to develop AHR to exercise.

PATHOGENESIS

The stimulus for EIB is a consequence of the increased airflow that accompanies whole-body exercise. Figure 3 depicts the cascade of events leading to EIB and the cellular and functional changes that cause airway narrowing. Pulmonary gas exchange requires that the inhaled air be warmed to 37°C and saturated with water before it reaches the alveolar gas exchange regions of the lungs. At rest and during light to moderate exercise, inhaled air is readily conditioned in the first few airway generations. At moderate to vigorous exercise intensities, however, the high ventilatory volumes challenge the capacity of the conducting airways and their thin layer of surface liquid to condition the inspirate. Thus, excessive evaporative airway water loss may occur, which causes a concurrent increase in airway osmolarity (31,32). Given that osmotic balance must be maintained between the airway surface and the adjacent cells of the airway walls, water flux from resident cells (i.e., epithelial cells) and nonresident inflammatory cells (i.e., mast cells and eosinophils) occurs. Through cellular mechanisms that are beyond the scope of this review (33), the cell water loss stimulates release of preformed proinflammatory mediators from nonresident inflammatory cells, particularly mast cells and eosinophils. Such mediators include the leukotrienes, prostaglandins, and histamine, which cause airway smooth muscle contraction, increased capillary permeability with plasma exudation and airway wall edema, and mucus cell hypersecretion. As a result, the airways narrow, airway resistance increases, and the widely described clinical symptoms of chest tightness, shortness of breath, wheeze, and cough are manifested.

It is generally accepted that release of proinflammatory mediators is the predominant cause of EIB. However, the airway narrowing may also be exacerbated by a rapid postexercise swelling of the airway wall secondary to thermal events associated with increased airflow (34). During exercise, increased airflow causes cooling of the airway mucosa and vasoconstriction of the bronchial circulation. Following exercise, ventilation and airflow decrease rapidly, which causes a correspondingly rapid increase in bronchial blood flow and airway temperature (35). The rapid increase in bronchial blood flow (so-called reactive hyperemia) may overwhelm the integrity of the vascular endothelium such that plasma extravasation and subsequent mucosal edema occur; the airways might then narrow secondary to physical encroachment of the airway walls into the lumen (35). The key pathophysiological alteration that accounts for the postexercise obstructive response in persons with asthma—whereas airway narrowing does not occur in persons who are nonasthmatic—is both an increased surface area and increased reactivity of the bronchial vasculature in persons with chronic asthma (36–38).

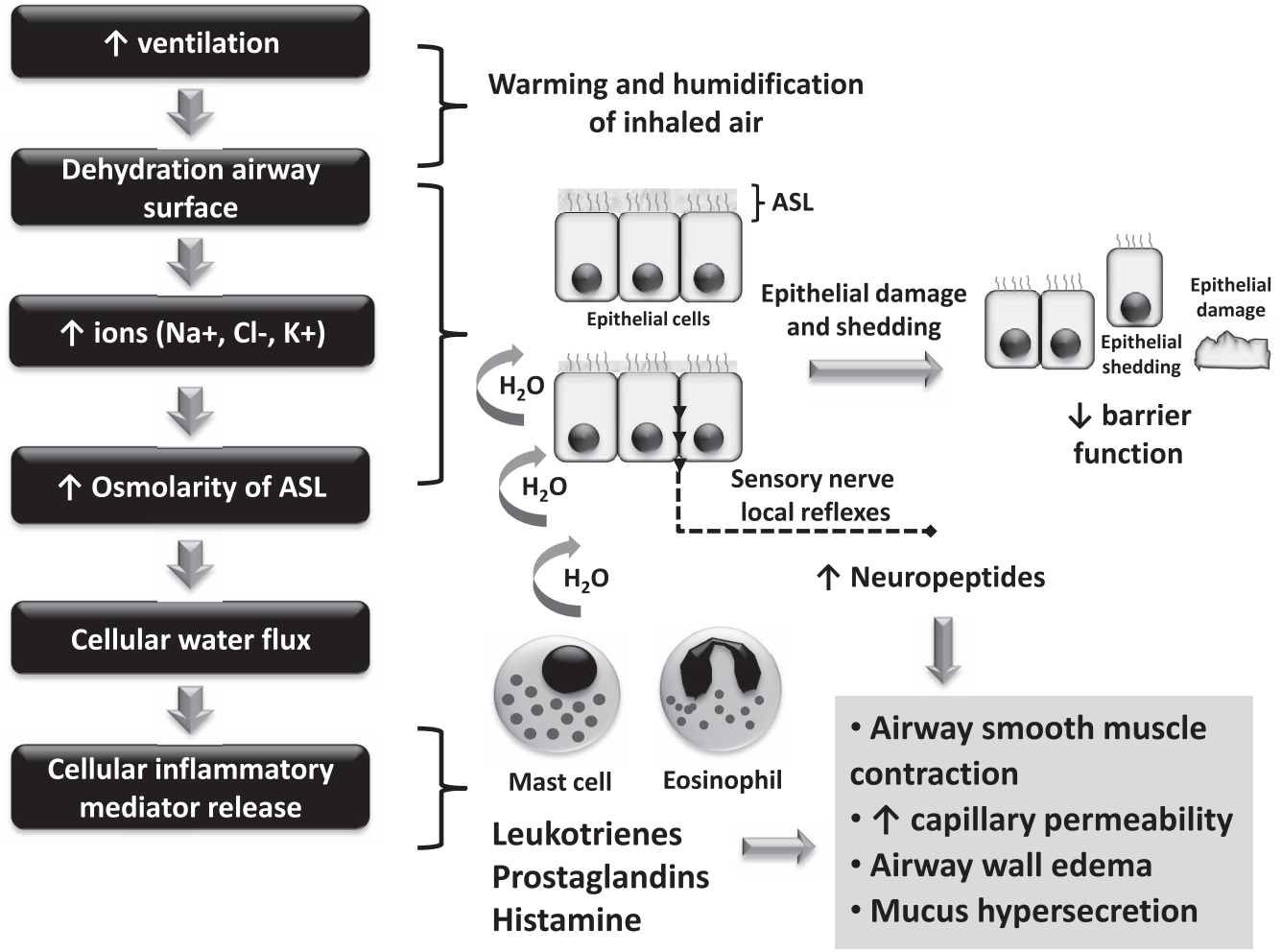
DIAGNOSIS

EIB may be diagnosed with an exercise challenge or a eucapnic voluntary hyperpnea challenge. The choice of diagnostic test depends on the equipment available, the training and expertise of the clinicians, and the characteristics and preferences of the patient.

Pre-Challenge Considerations

Baseline pulmonary function must be within safe limits prior to any challenge testing. In general, pulmonary function

FIGURE 3. General overview of the pathophysiological mechanisms for exercise-induced bronchoconstriction (EIB). Increased airflow with exercise causes dehydration of the airway surface and a resulting increase in the osmolarity of the airway lining fluid. This homeostatic disturbance causes cellular water flux and release of pre-formed and synthesized proinflammatory mediators from resident and nonresident airway cells. Through several mechanisms, the mediators cause the airways to narrow, increase airway resistance, and result in the clinical symptoms of wheeze, cough, chest tightness. and shortness of breath. Overall flowchart is from Anderson and Daviskas (33). Other references support mechanisms (88–92) . ASL indicates airway surface liquid.

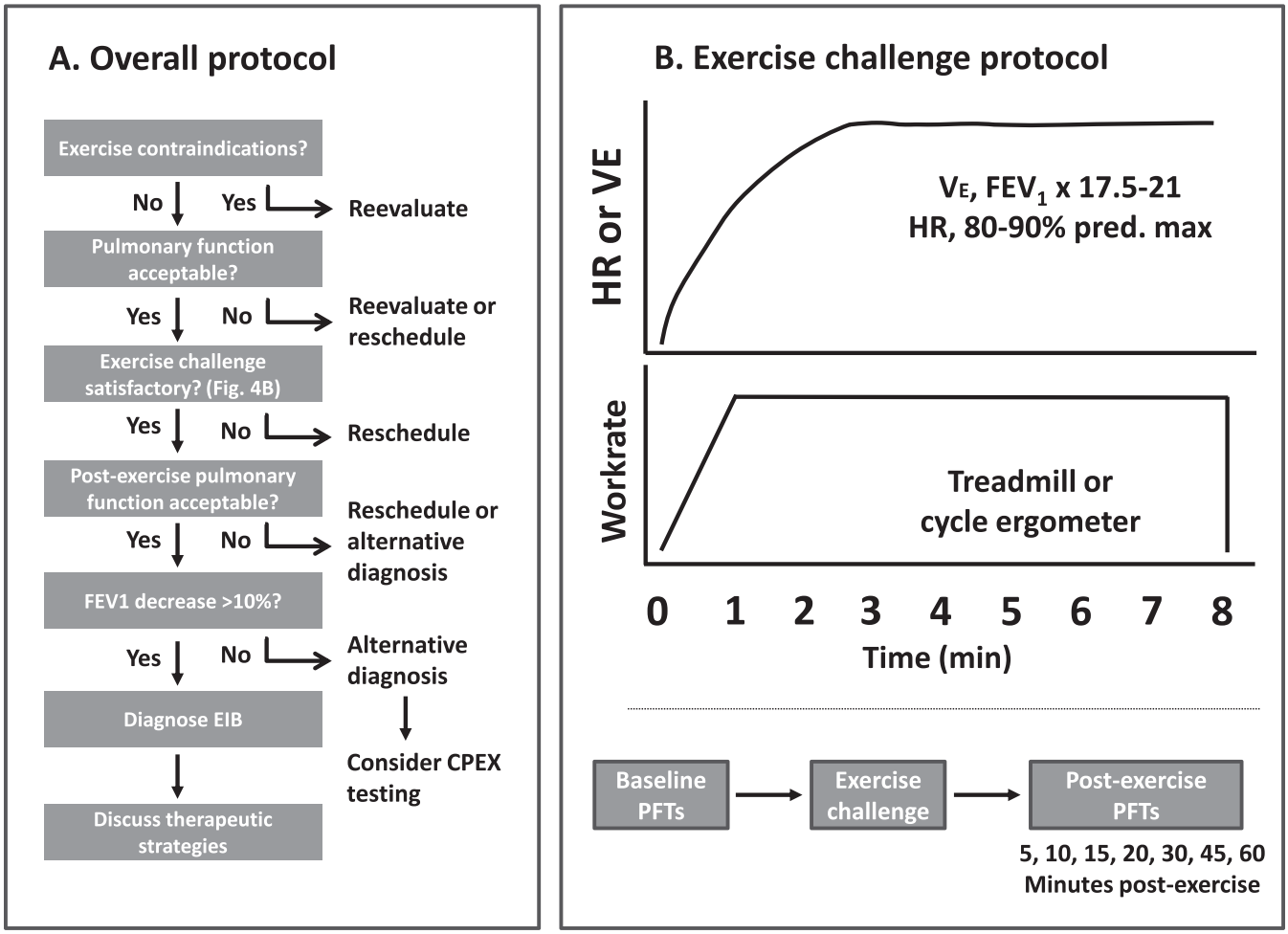


should be repeatable and within 75% of predicted values (39). Avoidance of a variety of medications should also be considered prior to testing for presence of EIB. Short- and long-acting β_2-agonists, anticholinergics, cromolyn sodium and nedocromil, antileukotrienes, antihistamines, and inhaled steroids should all be withheld for appropriate periods of time prior to challenge testing. However, this does not apply if the purpose of the challenge is to assess the efficacy of pharmacologic treatment.

Exercise Challenge

The most specific procedure for diagnosing EIB is to assess pulmonary function before and after an exercise challenge using a cycle ergometer or motorized treadmill. Figure 4A and B depict the protocol for assessing EIB via an exercise challenge. The overall protocol consists of baseline spirometry (generally forced vital capacity maneuvers), an acute exercise bout between 6 and 8 min in duration, and postexercise spirometry performed at regular intervals for at least 30 min following the exercise. The goal of the exercise challenge is to rapidly increase ventilation ($\dot{V}E$) to a high fraction of ventilatory capacity and to maintain such $\dot{V}E$ for an additional 4–6 min. General guidelines recommend a target $\dot{V}E$ of at least $FEV_1 \times 17.5$–21 (7), where FEV_1 has been measured prior to exercise. Alternatively, heart rate may be used as the metric of exercise intensity, in which case a value of 80% to 90% predicted maximum is recommended. Exercise workload should be increased to a predetermined level within 15–60 seconds, and thereafter titrated to meet the necessary $\dot{V}E$ or heart rate. Bear in mind that the likelihood that exercise will stimulate EIB is highly related to the $\dot{V}E$ achieved and sustained. In our lab, we set work rate at 85% of the peak power achieved during an incremental exercise test-to-exhaustion. Work rate is increased rapidly during the first 15 seconds of exercise. In our experience, most, but

FIGURE 4. (A) General flowchart of protocol used to diagnose exercise-induced bronchoconstriction (EIB). (B) Schematic of the exercise protocol for assessing EIB. A 6- to 8-min exercise bout is preceded and followed by serial spirometry. Exercise workload is increased rapidly until the patient reaches the predetermined value for heart rate or minute ventilation (VE); the workload is subsequently altered to maintain this value. The inspirate may be room air or gas from a compressed air tank. Given the mechanism for EIB, dry gas is more likely to stimulate airway narrowing and will result in a more sensitive test for EIB. CPEX indicates cardiopulmonary exercise testing; HR, heart rate; PFT, pulmonary function test.



not all, persons are able to complete 6 min of exercise at this intensity.

At the onset of exercise, an initial bronchodilation occurs in the majority of persons with asthma, especially in those with baseline airway obstruction that is at least partially reversible (40,41). At a constant exercise workload, a modest yet progressive bronchoconstriction may occur after approximately 10–15 min of exercise (42). Moreover, increased exercise duration necessitates a reduced workload, which not only decreases the stimulus for EIB (i.e., high airflow) but also may induce some refractoriness to airway narrowing (16). Thus, exercise duration should be between 6 and 8 min and of adequate intensity, with its onset and termination occurring in a nearly square-wave pattern.

The inspirate during an exercise challenge may be ambient air or air that has been dried or cooled. EIB severity is increased when the inspirate is cold (17), dry (43), or both cold and dry (44,45). Under conditions of cold or dry air, the osmotic and thermal events that stimulate EIB are further magnified. Compressed gas from a tank may be used to deliver dry air. Compared with the relative ease of delivering dry air to the inspired tubing, it is more challenging from a technical standpoint to cool the inspirate. However, devices have been used that can alter air temperature and humidity (45,46). A climate chamber or outdoor exercise in regions with cold winter temperatures may also be used. In any case, the condition of the inspirate has an important influence on the likelihood of stimulating EIB in susceptible persons.

Eucapnic Voluntary Hyperpnea Challenge

The provoking stimulus for EIB is increased ventilation and a resulting excessive evaporative water loss from the airway surface fluid. Thus, voluntary hyperpnea in the absence of whole-body exercise—is an effective procedure for assessing AHR to exercise. Indeed, similar degrees of airway narrowing occur following whole-body exercise and eucapnic voluntary hyperpnea in patients with asthma (8). In this procedure, patients voluntarily ventilate at a predetermined

$\dot{V}E$ for 6 min while remaining in a seated position. The target $\dot{V}E$ is typically calculated as $FEV_1 \times 30$ (47). To prevent hypocapnia, air with increased carbon dioxide from a compressed gas tank is used as the inspirate (5% CO_2, 21% O_2, balance nitrogen). Moreover, the compressed gas is relatively dry, which is significantly more asthmogenic than more humid room air.

Outcome Measures

The standard forced vital capacity (FVC) maneuver is the most commonly employed procedure to assess EIB. The FEV_1 is used to diagnose EIB, determine its severity, and assess response to treatment. Historically, peak expiratory flow has also been used as the outcome measure to determine EIB; however, the effort-dependence (i.e., motivation and coordination) of this index makes it an undesirable outcome measure. Other measures of mid-expiratory flow may be used to supplement FEV_1 and FVC, but they should not be used as the criterion measure for diagnosing EIB.

Due to the interdependence between the lung parenchyma and the intrapulmonary airways, the inhalation to total lung capacity during an FVC maneuver may cause an acute bronchodilation, especially under bronchoconstricted conditions (48). Thus, FEV_1 may slightly underestimate the actual extent of airway narrowing. Forced exhalations from end-inspiratory lung volume (i.e., partial forced exhalations) avoid the bronchodilatory effect of a deep breath and have been used to evaluate airway function responses to exercise (49). However, the technical and interpretive shortcomings of this technique make it unsuitable in most situations.

The forced oscillation technique (FOT) is an effort-independent procedure for assessing airway function that does not require a full lung inhalation. Briefly, an oscillating flow signal is applied to the airway opening during tidal breathing while the corresponding pressure signal is measured; the relationship between airflow and airway pressure is used to calculate input impedance and respiratory resistance (50). The principle advantage of the FOT is that airway resistance may be assessed during tidal breathing, thus avoiding a volume history effect on airway caliber. Moreover, respiratory resistance from the FOT may be more sensitive than FEV_1 for diagnosing AHR to whole-body exercise (51,52). However, the clinical relevance and reliability of the FOT have not been adequately studied, and the technique should be interpreted with caution and used in conjunction with spirometry when possible.

Variables Moderating EIB

Three important variables interact to determine the asthmogenicity of an exercise bout. First, both the rate of rise in $\dot{V}E$ and the $\dot{V}E$ achieved are critical determinants of the likelihood for exercise to cause bronchoconstriction in susceptible persons. EIB severity is thus highly related to the level of ventilation during an exercise session (10,53,54). Additionally, gradual increases in $\dot{V}E$ are less likely to stimulate airway narrowing compared with more rapid increases in $\dot{V}E$ (55). It might be the case that gradual increases in $\dot{V}E$ minimize the airway osmotic or thermal disturbances that stimulate EIB. Similarly, gradual increases in airflow may provide more time for protective airway responses that combat airway narrowing.

Second, the duration of exercise must be sufficient to challenge airway homeostasis for cellular water balance. In general, $\dot{V}E$ must be increased for at least 3 to 4 min to stimulate EIB (10,53). On the other hand, prolonged exercise lasting longer than 10 min is less likely to cause significant bronchoconstriction than shorter bouts. There are a couple of potential explanations for this. First, airway cells may release biological mediators that protect against airway narrowing (56). Second, prolonged exercise necessitates decreases in exercise workload and therefore decreases in $\dot{V}E$. Thus, the stimulus for airway narrowing—$\dot{V}E$—may not be high enough to adequately disturb the airway environment.

Third, the condition of the inspirate has a profound effect on EIB. Cool and dry air is more likely to cause EIB compared with air that is warmer and more humid (54,57,58). This reflects the greater loss of water and heat from the airway surface required to condition colder and dryer air, thus stimulating more severe airway narrowing in a person with asthma.

Differential Diagnosis

A number of clinical conditions may masquerade as EIB. Thus, in patients who experience breathing-related symptoms during or after exercise but with an absence of bronchoconstriction, a variety of alternative diagnoses must be considered. These differential diagnoses have been reviewed in detail elsewhere (14). Exercise-induced laryngeal obstruction (EILO) is a particularly prevalent condition that is far too often misdiagnosed as EIB. EILO is a broad diagnosis that encapsulates extrathoracic airway narrowing of any cause. Paradoxical inward movement of the vocal cords (i.e., vocal cord dysfunction), laryngeal prolapse, collapse of the arytenoids, and structural abnormalities of the glottis, among others, are all potential causes of EILO. An inspiratory stridor is a clear differentiating characteristic of EILO, often accompanied by a choking sensation in the throat. Additionally, the inspiratory limb of the exercise flow-volume loop is either truncated or displays a sawtooth or other abnormal pattern (59). However, a definite diagnosis of EILO requires laryngoscopic evaluation during exercise. Many other differential diagnoses exist, including physical deconditioning, idiopathic hyperventilation, restrictive lung disease, exercise-induced anaphylaxis, cardiac disease, psychological factors, and others (14). It is very important to bear in mind that the symptoms of EIB are largely nonspecific. Thus, diagnosing EIB based on medical history and a physical examination (in the absence of an exercise or eucapnic voluntary hyperpnea challenge) will result in many false-positives, especially as there are so many potential causes of dyspnea with exercise.

MANAGEMENT

The goals of therapy are to reduce the severity of bronchoconstriction and symptoms so that an athlete or patient with EIB can participate in any activity, irrespective of intensity or duration, without experiencing serious respiratory limitations. The treatment of EIB can be divided into pharmacologic and nonpharmacologic therapy.

Pharmacologic Therapy

Reliever (Quick-Relief) Medications

Quick-relief medications are used to relieve acute asthma exacerbations and to prevent EIB symptoms. The most frequently used reliever medications include short-acting β_2-agonists (SABAs) and anticholinergics. To prevent or minimize symptoms of EIB, the most frequent recommendation is the prophylactic use of SABAs (e.g., albuterol) prior to exercise. SABAs work by stimulating β_2-receptors in the airways causing bronchodilation as well as possibly inhibiting mast cell degranulation. Inhaling a SABA 5–20 min before exercise is usually effective in protecting against EIB for 2–4 h (60). It should be noted that the daily use of SABAs, alone or in combination with inhaled corticosteroids (ICSs), may lead to tolerance, as documented by a lessening in the duration of protection against EIB (61), and for this reason it is recommended that SABAs only be used on an intermittent basis for prevention of EIB.

Short-Acting Inhaled Anticholinergics

These drugs (e.g. ipratropium bromide) work via competitive inhibition of muscarinic cholinergic receptors resulting in bronchodilation. Ipratropium bromide use has been shown to have variable effects in the degree of protection against development of EIB (7); in particular, the therapeutic response is related to the time of day, and the bronchoprotective effect appears to be inconsistent among patients with EIB and may be variable in the same patient (62,63). Due to its delayed onset of action, ipratropium bromide should not be used as a quick-relief inhaler; SABAs are indicated for rapid reversal of bronchoconstriction.

Controller (Long-Term Control) Medications

Common long-term control medications used to treat EIB are ICSs, long-acting $\beta_2$agonists (LABAs), leukotriene receptor antagonists (LTRAs), antihistamines, and sodium cromoglycate and nedocromil sodium. ICSs have proved to be effective in the treatment of asthma and are the mainstay of asthma therapy in athletes due to their multiplicity of anti-inflammatory actions (7,64). Studies of ICSs have shown that it may take up to 4 weeks for the maximum beneficial effect in protecting against EIB (7). ICSs can be used alone or in combination with other pharmacotherapies for EIB. The most common strategy to treat athletes with asthma or EIB is daily treatment with ICSs, with SABAs used only occasionally prior to exercise (64). ICSs, beginning with a low dose, should be considered if a patient needs to use a SABA more than twice per week—including doses required to prevent EIB—or if asthma is limiting exercise tolerance (64).

Long-Acting β_2-Agonists

LABAs (e.g. formoterol) have been shown to be effective in preventing EIB (65); however, similar to SABAs, their effectiveness decreases with daily use (66–68). These agents can initially protect against EIB for 6–12 h; however, after daily use for 30 d the effect diminishes to 6 h (67). Concomitant daily use of ICSs does not mitigate the loss of effectiveness with daily use (66,68). Therefore, daily LABA monotherapy is not recommended due to an increased rate of treatment failures and acute exacerbations being documented in clinical trials (7). In addition, there is a serious concern regarding mortality and morbidity with any use of LABA as monotherapy, without concomitant use of ICSs in patients with asthma (7).

Leukotriene Receptor Antagonists

LTRAs taken daily (montelukast sodium) have a protective effect against EIB and improve recovery time to baseline (7). Although the magnitude of protection against EIB may be less than that of either ICSs or SABAs, the duration of action is longer, up to 24 h, which is useful for athletes who are engaged in multiple training bouts throughout the day (69,70). LTRAs offer protection against EIB regardless of whether individuals have classic asthma or are athletes without asthma (71). However, montelukast sodium generally provides only about 60% protection against EIB, and not all patients will benefit from this amount of protection (72). For maximal prophylactic effect these agents should be taken 2 h prior to exercise (69). There is no development of tolerance when LTRAs are taken daily (73).

Antihistamines

These drugs (e.g., loratadine) provide some protection against EIB in a small percentage of patients (74,75). Daily antihistamine use in patients with allergy may be helpful in EIB; however, it is recommended that patients without allergies refrain from taking daily antihistamines to control their asthma, since this agent does not appear to confer any significant benefits in these patients (7).

Mast Cell Stabilizing Agents (MCSAs)

MCSAs, such as sodium cromoglycate and nedocromil sodium, provide protection against EIB with an attenuation of EIB by ~50% (76,77). These agents block degranulation of mast cells and mediator release, such as prostaglandin D_2 (7). MCSAs appear to be more effective than anticholinergic agents, but less effective than SABAs, in attenuating EIB (7). It should be noted that although MCSAs are available worldwide, nedocromil sodium is not available in the United States.

It is very important that athletes with asthma or EIB adhere to the World Anti-Doping Agency regulations pertaining to the use of asthma medications. For example ICSs, LTRAs, inhaled anticholinergics, antihistamines, and sodium

cromoglycate and nedocromil sodium are permitted and do not require a therapeutic-use exemption (63,64). Oral corticosteroids are prohibited during competition only, and all β_2-agonists are prohibited except inhaled salmeterol, formoterol, and albuterol when used in accordance with World Anti-Doping Agency guidelines (64). Clinics and laboratories involved in assessing AHR in athletes (required for a β_2-agonist therapeutic-use exemption) must be particularly rigorous in implementing test procedures and spirometry so that both false-positives and false-negatives can be minimized.

Nonpharmacologic Therapy

Nonpharmacologic therapy includes breathing through a face mask or scarf to humidify and pre-warm air during exercise, high-intensity warm-ups performed prior to exercise training or competition, improvement in physical conditioning, weight loss, and nutritional intervention. A face mask (78), and a heat-exchanger mask (79) have been used to pre-warm and humidify inhaled air during exercise—the premise behind using these techniques is that EIB occurs as a result of the drying and cooling of the airways during vigorous exercise. It is recommended, based on a small number of studies, that individuals with EIB who exercise in cold weather use a mask that humidifies and warms the air during exercise (7), and use a face mask to reduce the effects of the inhalation of particulate air pollutants for athletes with EIB who are training and competing in indoor skating rinks and urban areas with high traffic emissions (80).

A key strategy that can be used to lessen EIB is to engage in a physical warm-up before training or competition. The warm-up typically consists of 10–15 min of moderate to vigorous exercise, resulting in the subsequent amount of bronchoconstriction being reduced for the next 2 h; this is termed the "refractory period" (41,81). This phenomenon does not occur in all individuals with EIB; rather, refractoriness to bronchoconstriction seen with more than one exercise bout occurs in approximately 50% of those with EIB (41,82,83).

An improvement in general physical conditioning may attenuate EIB (84). This likely occurs as a result of a lower $\dot{V}E$ required for any given workload once an improvement in aerobic fitness has occurred. Improved aerobic fitness may be particularly effective in persons who are overweight (85). In addition, there is evidence that weight loss (86) and nutritional intervention, such as the adoption of a low-sodium diet, and supplementation with omega-3 fatty acids and vitamin C, may lessen the severity of EIB (7,87).

SUMMARY

EIB bronchoconstriction refers to airway narrowing that occurs after exercise in any person, irrespective of the presence of clinically diagnosed asthma. Clinically, EIB is diagnosed by a decrease in FEV_1 of at least 10% following whole-body exercise. The vast majority of patients with asthma are susceptible to significant airway narrowing with exercise, but variable airway inflammation—and thus disease activity—result in variable susceptibility to EIB over time. Among the general population, the prevalence of EIB is approximately 10%; however, habitually active people have a higher incidence of EIB, and it is particularly increased in athletes competing in aerobic events that require high ventilation. The primary stimulus for EIB is the increased pulmonary airflow with exercise, along with the requirement that the air be fully conditioned by the time it reaches the gas exchange regions of the lungs. EIB can be diagnosed with an exercise challenge or a voluntary hyperpnea challenge; both challenges demand increased ventilation and stimulate airway narrowing via the same mechanism. There are a variety of pharmacologic options for treating EIB, depending on the characteristics of the individual. There are also a number of nonpharmacologic approaches that should be considered in all cases of EIB. Finally, the symptoms of EIB are largely nonspecific, and there are many additional potential causes of respiratory symptoms with exercise. Thus, diagnosing EIB based solely on medical history and a physical examination is normally not recommended.

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