Drugs 2002; 62 (12): 1725-1739
0012-6667/02/0012-1725/$30.00/0

Exercise-Induced Bronchoconstriction

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Abstract

Exercise-induced asthma, or more appropriately, exercise-induced bronchoconstriction (EIB), occurs in 80 to 90% of individuals with asthma and in approximately 11% of the general population without asthma. EIB is characterised by post-exercise airways obstruction resulting in reductions in forced expiratory volume in 1 second (FEV_1) of greater than 10% compared with pre-exercise values. The mechanism of EIB remains elusive, although both cooling and drying of airways play prominent roles. Cold, dry inhaled air during exercise or voluntary hyperventilation is the most potent stimulus for EIB. Inflammatory mediators play central roles in causing the post-exercise airways obstruction.

Diagnosis of EIB requires the use of an exercise test. The exercise can be a field or laboratory based test, but should be of relatively high intensity (80 to 90% of maximal heart rate) and duration (at lest 5 to 8 minutes). Pre- and post-exercise pulmonary function should be compared, and post exercise pulmonary function determined over 20 to 30 minutes for characterisation of EIB. A pre- to post-exercise drop in FEV_1 of greater than 10% is abnormal.

Approaches to treatment of EIB include both nonpharmacological and pharmacological strategies. A light exercise warm up prior to moderate to heavy exercise reduces the severity of EIB. More recently, studies have supported a role for dietary salt as a modifier of the severity of EIB, suggesting that salt restrictive

diets should reduce symptoms of EIB. Short acting, inhaled β_2-agonists constitute the most used prophylactic treatment for EIB. However, antileukotriene agents are emerging as effective, well tolerated, long-term treatments for EIB.

1. Introduction

Exercise-induced asthma (EIA) is a term commonly applied to exercise-related airways obstruction documented post exercise. Other terms that apply to the same phenomenon are exercise-induced bronchoconstriction (EIB), exercise-induced airways obstruction (EIAO), and hyperpnoea-induced airways obstruction (HIAO). While EIA has been the widely used term, EIB has now become the term used in the research literature and is more accurate in describing this phenomenon. EIB will be used in this review as the most descriptive term for this condition.

1.1 Characteristics of Exercise-Induced Bronchoconstriction (EIB)

EIB is typically characterised as a reduction in post-exercise pulmonary function. This is generally expressed as a percent reduction in forced expiratory volume in 1 second (FEV_1), pre- to post exercise, as shown in figure 1 and figure 2. Maximal expression of EIB is generally 3 to 10 minutes post exercise.[1,2] A refractory period of up to 3 hours after recovery from exercise, during which repeat exercise causes less bronchospasm, has been observed. Airways obstruction can often be identified during the exercise, if the exercise is of longer duration or the individual is more sensitive.[3] Long distance runners often report the ability to 'run through' an attack, with little or no post-exercise decrement in pulmonary function; although this phenomenon has not been examined experimentally.

EIB is 'self limiting' in that the reductions in pulmonary function, although often severe, dissipate over 30 minutes to an hour,[2] with late-phase responses being less common. This is in contrast to antigen-induced asthma, which often requires medical intervention in order to limit the attack. There are no literature reports of an exercise-related death caused specifically by EIB. Again, in marked contrast to antigen-induced asthma, which can be fatal. However, any individual with hyperactive airways such as those with asthma may be at increased risk during the hyperpnoea of exercise, as the allergen load is increased. The recent death of an asthmatic Northwestern University athlete during football practice emphasises this risk.[5]

1.2 Epidemiology of EIB

The prevalence of EIB in the general population is unknown. However, it is generally considered that 80 to 90% of individuals with asthma, 40% of those with allergic rhinitis, and 12 to 15% of the general population experience EIB[6-8] with moderate exercise. It is likely that all individuals with asthma will experience EIB if the exercise intensity and duration are sufficient. In a survey of 1984 Olympic athletes, approximately 11% of US athletes experienced EIB.[9] More recently, Wilbur et al.[10] surveyed the 1998 US Winter Olympic Team. They found that the overall incidence of EIB across all sports and genders was 23%. The highest

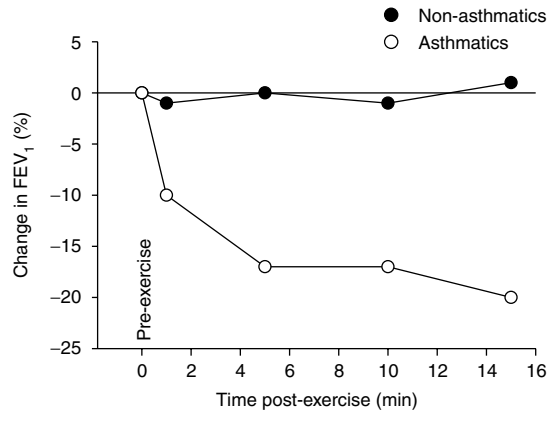

Fig. 1. Percent change in forced expiratory volume in 1 second (FEV_1) pre- to post exercise in patients with asthma versus individuals without.[4]

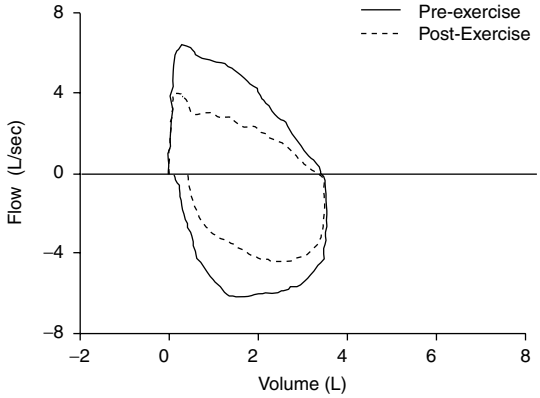

Fig. 2. Flow-volume loops of forced vital capacity, before and after exercise in patients with exercise-induced bronchospasm.

incidence of EIB was found in cross-country skiers, where 50% of the athletes (female = 57%; male = 43%) were diagnosed with EIB. Across the seven sports evaluated, the prevalence of EIB among the female and male athletes was 26 and 18%, respectively. In a screening study of 214 high school football players, 9% demonstrated EIB.[11] Correspondingly, in a screening study of 166 middle and high school athletes, 13% demonstrated EIB.[12] The incidence of EIB has been reported to be as high as 19.3% of Australian school children.[13] Therefore, EIB is a significant finding in both asthmatic and non-asthmatic populations.

Interestingly, recent studies have suggested that athletes performing high levels of training in cold, dry climates may have chronic airway inflammation as a result. Karjalainen et al.[14] evaluated both asthmatic and non-asthmatic cross-country skiers for the presence of airway inflammation and hyperresponsive airways. Inflammatory changes were present irrespective of asthma-like symptoms, hyper-responsiveness, or atopy. They concluded that prolonged repeated exposure of the airways to inadequately conditioned air might induce inflammation and remodeling in competitive skiers. Davis and Freed[15] used a canine model to expose airways to repeated exposure of cold, dry air via hyperpnoea on 5 successive days. They found increased markers for airway inflammation and reduced response to β-agonists. They concluded that repeated dry air exposure with hyperpnoea causes peripheral airways inflammation, obstruction, hyper-reactivity, and impaired β-agonist–induced relaxation. This suggested that other mechanisms in addition to increased smooth muscle tone might contribute to the development of repetitive hyperpnoea-induced bronchial obstruction and hyperreactivity. While these studies may be describing an entity separate from EIB, there remains the possibility that high levels of training might contribute to development of chronic airway inflammation.

1.3 Objectives

Exercise was one of the first stimuli recognised as an initiator of airway obstruction characteristic of asthma. EIB is of clinical interest because the ability to exercise without severe limitation is important in maintaining fitness and health, and in the accomplishment of activities of daily living. In addition, EIB may be a marker of a yet to be expressed asthmatic condition. While exercise does not cause asthma, it is part of the asthmatic diathesis where exercise is one of many stimuli that induce airflow limitation. Thus, the diagnosis and treatment of EIB is important clinically not just for athletic performance but also in the early recognition of potential early manifestation of more severe airways disease.

The purpose of this review is to consider the potential mechanisms by which physical exertion results in obstruction of the airways, to highlight acceptable methods of diagnosis, and to provide contemporary treatment options. In completing this review, articles found through a search of Medline and SportDiscus databases using the term exercise-induced asthma or exercise-induced bronchoconstriction were selected for inclusion.

2. Mechanisms of EIB

For studying the potential mechanisms by which exercise results in reduced airway calibre, several potential questions for investigation can be identified (figure 3). The first is the stimulus, what is it about exercise that initiates the attack? Sec-

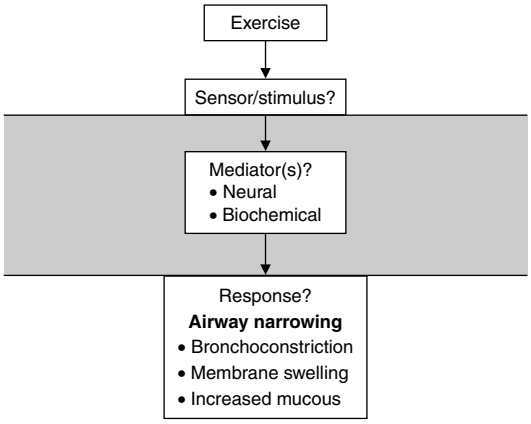

Fig. 3. Schematic of potential sites for mechanisms of exercised-induced bronchospasm.

ondly, how is the stimulus sensed or transduced into a physiological signal? Thirdly, what neural, biochemical or other pathway(s) serves as mediator for the stimulus to the response? Finally, is the response contraction of smooth muscle, swelling of the mucosal lining of the airways, increased mucous production, or some combination(s) of these effects?

2.1 Stimulus and Sensation

With respect to the exercise stimulus responsible for the EIB response, the hyperpnoea of exercise plays a substantial, if not complete, role as the initiating stimulus. In fact, voluntary hyperpnoea and exercise are often used interchangeably to induce airway obstruction in individuals with asthma.[16] Isocapnic hyperpnoea is preferred as hyperpnoea-induced hypocapnia may produce chest discomfort perceived as dyspnea without bronchospasm.[17] However, Suman et al.[18] cast doubt on exercise and isocapnic hyperpnoea as equivalent stimuli for inducing changes in airway function in EIB. They focused on changes in airway function during exercise or during hyperpnoea, in which case exercise induced greater decrements in airway function during the exercise. Post-exercise reductions in pulmonary function, however, were similar for the two stimuli. Based on the literature, it seems reasonable that hyperpnoea is the key stimulus for EIB; although other variables may modify the EIB response associated with the exercise *per se*, such as increased body temperature and increased bronchiolar circulation.[19]

Respiring cold, dry air remains the most potent stimulus for EIB. Stemming from this fact, two main theories as to the mechanism by which the hyperpnoea of exercise is translated into a stimulus for initiating the EIB response have emerged. McFadden et al.[20-25] and Anderson et al.[26-30] have, respectively, proposed the heat loss and water loss/osmotic theories of EIB. The heat loss, airways cooling, theory would suggest that heat loss from the airways during exercise, and possibly the rewarming of the airways post-exercise, serves as the stimulus for EIB. In contrast, the water loss/osmotic, airways drying, theory addresses the loss of water from the airways during exercise, and the likelihood that this increases the osmolality of pericellular fluid resulting in EIB. Difficulty in separating the temperature and humidity of the airways during experimental studies has limited the interpretation of results. Clearly, both are provocative stimuli. For example, both exercise and drinking ice water have been shown to induce airways obstruction[31] in those susceptible. In addition, inhalation of a hyperosmotic saline solution results in airways narrowing.[32] Recently, Anderson and Daviskas[30] have attempted to merge the two theories by suggesting that the inspiration of cold air not only cools the airways but also increases the number of airway generations becoming dehydrated in the humidifying of the inspired air. While the specific stimulus, heat loss or water loss, is still controversial, both likely play a major role in inducing EIB, and modifying both variables controls the symptoms.

2.2 Mediators

In attempting to address possible mediators of airways cooling and/or water loss, neural and biochemical factors have been studied. While a vagovagal reflex that could react to airway irritation and respond with bronchoconstriction has been sug-

gested, there are few data to support this concept. Arguing against such a reflex, prior anaesthesia of the bronchiole tree did not prevent the airways restriction of exercise or that to isocapnic hyperventilation.[33,34]

Although human airways are not innervated by adrenergic supply, circulating catecholamines can stimulate airway β_2-adrenoreceptors and cause bronchodilation (and inhibit mast cell mediator release), an important mechanism for bronchodilation during exercise in healthy volunteers. It has been suggested that an impaired sympathoadrenal response to exercise may facilitate bronchoconstriction in individuals with EIB, either via reduced counter dilation or reduced inhibition of mast cell mediator release. However, there are no substantive data to indicate that those with EIB have reduced sympathoadrenal responses to exercise.[35]

In contrast to the evidence with regard to neural mediation of EIB, there is voluminous data supporting varied biochemical factors as mediators of the EIB response. Mast cells, along with eosinophils, neutrophils, basophils, lymphocytes and macrophages, constitute potential sites for synthesis of inflammatory and bronchoconstricting agents. The role of mediator release in EIB has been investigated by detecting the mediators in body fluids following exercise challenge, and by determining the effect of specific antagonists or inhibitors of synthesis on the exercise-induced airway response. Although the data provide strong evidence for the involvement of an inflammatory cascade in EIB, and identifies major contributing mediators, the total picture has not been delineated.

Histamine release from mast cells has been extensively studied. The fact that sodium cromoglycate and nedocromil, inhibitors of mast cell mediator release, are effective in preventing EIB suggests mast cell involvement. Histamine H_1 receptor antagonists demonstrate 30 to 50% protection in EIB.[36,37] However, it has been difficult to consistently demonstrate increased histamine release in individuals with EIB either in blood or in bronchoalveolar lavage fluid.[38]

Prostanoids derived from the cyclo-oxygenation of arachidonic acid constitute prostaglandins and thromboxane A_2 (TxA_2). Prostaglandin (PG)D_2, $PGF_{2\alpha}$, and TxA_2 are potent bronchoconstrictors, whereas PDE_2 and PGI_2 are bronchodilators. Thus, a potential imbalance in release of these agents could contribute to EIB. Use of cyclo-oxygenase inhibitors and thromboxane synthesis and receptor antagonists have not consistently demonstrated a significant role for bronchoconstricting PGs or TxA_2 in EIB.[39,40] The overall results suggest an attenuating effect on EIB of cyclo-oxygenase inhibition, but not with TxA_2 receptor inhibition. However, there is an apparent clear role for PGE_2, a bronchodilator, in contributing to the refractory period following EIB.[39]

The sulfidopeptide leukotrienes are produced by 5-lipo-oygenase actions on arachidonic acid, followed by conjugation with glutathione. Leukotriene (LT)C_4 is the initial product, followed by LTD_4 and LTE_4. Leukotrienes are all bronchoconstrictors in asthma, and are 100 to 1000 times more potent than histamine.[41] Specific cell receptors respond to leukotrienes. Numerous investigations on the role of leukotriene synthesis and action have led to the emerging acceptance of the central role of leukotrienes in the bronchoconstriction of both allergen-induced and exercise-induced asthma.[41-47] Mast cells are most likely the predominant source of leukotrienes released in EIB.[48] Eosinophils do not appear to play a major role in EIB, in contrast to allergen-induced asthma.[45] Monocytes and macrophages are also important sources of leukotrienes but any mechanisms for their activation with exercise are unknown.

In summary, there is sufficient evidence to suggest that the release of constrictor mediators, histamine, prostaglandins and leukotrienes is an important contributor to the bronchoconstriction induced by exercise and hyperventilation. The relative contribution of these mediators has not been determined and it is likely that the relative action of these mediators vary among individuals with EIB. Presumably, airway cooling and drying during exercise constitutes the stimuli for mediator

release. However, there may be a direct role for exercise as a stimulus[19] for mediator release; although this has been little studied. In addition, bronchodilating mechanisms may play a more significant role in modifying the action of these constricting mediators than previously thought. Agents such as mast-cell produced heparin and PGE_2, atrial natriuretic peptide, kinins, substance P, vasoactive intestinal peptide and other vasoactive agents may also play a modifying role in EIB, although much more investigation is required before specific roles can be assigned.

2.3 Response

While the majority of studies have focused on the concept that EIB constitutes a bronchoconstriction or bronchospasm, there is no direct evidence that bronchiolar smooth muscle indeed undergoes active contraction resulting in airways obstruction in EIB. While this is likely to be a major component of the airways obstruction, there is a suggestion that EIB may be a vascular phenomenon. That is, that vascular engorgement post-exercise and mucosal oedema results in the airways narrowing associated with EIB.[23] McFadden[23] has proposed that the cooling of the airways, and especially the rewarming of the airways post-exercise, results in a post-exercise hyperaemia and oedema. This engorgement of the airways restricts airflow. In addition, they suggest that this engorgement may increase bronchiolar smooth muscle reactivity to histamine and isocapnic hyperventilation. It is difficult to distinguish experimentally between bronchoconstriction and vascular engorgement in humans. Furthermore, increased mucus production in the airways in EIB could contribute to airways obstruction, although this has been little studied. Therefore, it is more likely to be some time before the actual mechanism for airways narrowing in EIB is fully described and it probably includes all three mechanisms to varying degrees.

2.4 Summary

Returning to figure 3, we can summarise the existing data with regard to the mechanisms of EIB. While exercise may provide multiple stimuli for EIB, hyperpnoea is the dominant stimulus for inducing EIB. Cooling and drying, and possibly rewarming, affect airways resulting in local multiple inflammatory mediator release of which histamine, prostaglandins and, especially, leukotrienes are important. Airways narrowing occurs post exercise as mediators, possibly along with rewarming, cause bronchoconstriction, vascular engorgement and leakage, and increased mucus production. The airways narrow progressively post exercise, peaking from 3 to 10 minutes typically. The obstruction dissipates over time, resolving in 30 to 60 minutes. This is followed by a refractory period of up to 3 hours that is dependent on prostaglandins that protect the airways from subsequent periods of exercise.

3. Diagnosis of EIB

Table I summarises the principal components in diagnosing EIB. Initially, an important distinction must be made: determining if the individual has chronic asthma or solitary EIB. Most, if not all, individuals with asthma will have EIB. However, those with solitary EIB do not usually have respiratory distress related to a non-exercise stimulant. Thus, a careful differential diagnosis with history and resting pulmonary function tests (PFTs) are required. Abnormalities in resting PFTs often support the presence of chronic, persistent asthma, while normal resting PFTs are more typical in individuals with solitary EIB. However, resting PFTs do not constitute the sole diagnostic criteria

Table I. Summary of diagnostic criteria for exercise-induced bronchospasm

History of coughing, wheezing, or shortness-of-breath with exercise
Positive exercise test - criteria based on percent decrement in post-exercise (1-15 min) FEV_1 with 5 minutes of exercise at 85-90% of maximum:
10% fall in FEV_1, abnormal
15% fall in FEV_1, most commonly used
20% fall in FEV_1, conservative
Relief of post-exercise airway obstruction with inhaled β-agonist

FEV_1 = forced expiratory volume in 1 second.

for the presence of asthma, in part because resting PFTs are often normal in between asthma attacks. Therefore, the presence of asthma *per se* should be based on well-recognised criteria such as those presented by, for example, the American Thoracic Society or the European Respiratory Society. Once it has been determined to exercise test for EIB, criteria (table I) are applied to PFTs to determine the presence or absence of EIB. Contraindications to exercise testing for EIB are shown in table II.

The type of exercise chosen to test for EIB often depends on resources available. Generally, there are two types of tests, field and laboratory. Field tests require little special equipment and have the ability to screen larger numbers of individuals in a short period of time. Free running is the most commonly used field test.[11] While the ability of any exercise test to detect EIB is dependent on parameters such as environmental conditions and exercise intensity and duration, field testing has proven adequate when performed to laboratory standards.[11,49]

The American Thoracic Society has published guidelines for exercise challenge testing for EIB.[50] These guidelines include extended contraindications and specific exercise criteria. Recently, Anderson et al.[51] have published guidelines for exercise testing for EIB using the cycle ergometer and breathing cool, dry compressed air. Both of these resources provide current, complete information for the establishment of a competent protocol for testing for EIB. In general, exercise of 6 to 8 minutes at 85 to 90% percent of maximal heart rate while orally breathing cool, dry air should be an adequate stimulus for eliciting EIB in those susceptible. FEV_1 is the primary outcome variable. Peak expiratory flow rate (PEFR) can also be used, although it is more effort dependent. PEFR is useful in field-testing because of convenience. PFTs are conducted before the exercise and at 5, 10, 15, 20 and 30 minutes post-exercise; although some included earlier, 1 and/or 3 minutes, measurements. A β_2-agonist inhaler may be used in the presence of appreciable dyspnoea or if the PFTs have not returned to within 10% of baseline when the individual is ready to leave the laboratory.

Table II. Contraindications to exercise testing for presence of exercise-induced bronchoconstriction

Uncontrolled asthma at rest
Wheezing at rest
Recent (6 weeks) viral/bacterial infection of upper or lower respiratory tract, sinuses or middle ear
Undiagnosed or untreated cardiac disease
Inability to perform spirometry or exercise

Typically, post exercise FEV_1 is expressed as a percent of pre-exercise value. A fall of 10% post-exercise is considered abnormal. Some consider a 15% reduction as diagnostic of EIB, while others use a 20% reduction as the required criteria.[50] Anderson[6] has suggested a schema of 10 to 25% reduction, mild EIB; 25 to 35% reduction, moderate EIB; 35 to 50% reduction, moderate to severe asthma; and over 50% reduction, severe EIB. This schema would be consistent with what is commonly reported in the literature.

It can be useful in diagnosing the severity of EIB to use the concept of the area under the curve, expressed as the area under the curve (AUC) defined by the percent fall in FEV_1 post exercise over time (see figure 1). Essentially, the longer and greater the depressions in the FEV_1 post exercise, the more severe is the EIB. More recently, Dahlen et al.[52] presented evidence that FEV_1 remained more reproducible and had more diagnostic power than did the AUC. Thus, it remains a preference of the diagnostician as to the use of the PFT measures.

It should be noted that those with upper airway abnormalities such as vocal cord dysfunction or abnormal movement of the arytenoid region might show similar reductions in FEV_1 as indicative of EIB. These can be differentiated through the use of flow-volume loops, and examining the characteristics.

For completeness it must be mentioned that it may be beneficial to measure FEV_1 *during* the exercise, as well. Since bronchodilation occurs with exercise, there may be some overshadowing of post exercise PFT decrements. Thus, it has been

suggested that an airway lability index, calculated as the maximum increase in FEV_1 during exercise minus the maximal post exercise fall in FEV_1 expressed as a percent of the pre-exercise value might be useful in some cases. This technique may uncover EIB in those individuals with depressed PFT at rest.[53]

4. Prevention/Treatment/Modifiers of EIB

The treatment of EIB is linked to preventing and/or modifying the severity of EIB and can be categorised into nonpharmacological modalities and pharmacological modalities (table III).

4.1 Nonpharmacological

The severity of EIB is altered by several modifiable nonpharmacological variables that can be used to prevent/treat/modify EIB. It has been long known that climatic conditions which alter the characteristics of the inspired air have a significant impact on post exercise pulmonary function in individuals with EIB.[54,55] Cold, dry air is the most potent stimulus for EIB. Thus, exercising in warmer, more humid conditions can reduce the severity of EIB. Swimming typically is associated with a lower prevalence of EIB,[56] although there are numerous swimmers with asthma. This may be a self-selection to this sport for the warm-humid air, or in part related to the presence of chlorine as an airway irritant. In contrast, figure skating has a high prevalence of athletes with EIB.[57]

Table III. Treatment and management of exercise-induced bronchoconstriction

Nonpharmacological
Climatic conditions: warm/humid *vs* cold/dry
Type of exercise: intensity, duration; continuous, intermittent
Refractory period: pre-exercise warm up protocols
Diet: caffeine, antioxidants, fish oil, salt (sodium chloride)
Pharmacological
Principal (inhaled):
short-acting β_2-agonists
long-acting β_2-agonists
sodium cromoglycate/nedocromil
Adjunctive (oral and inhaled):
theophylline
anticholinergics
furosemide
corticosteroids
anti-leukotriene agents

The type of exercise undertaken is also important in considering preventing or reducing symptoms of EIB. In general, the greater the intensity and duration of the exercise, the more severe is the EIB.[58] The concept of exercise load, intensity times duration, works well when considering EIB.[2] The minimum requirements for eliciting reproducible EIB appear to be exercise at 60 to 90% of maximal heart rate while running for 4 to 8 minutes.

Individuals with EIB typically demonstrate a refractory period after the initial post-exercise reductions in pulmonary function, returning to full susceptibility in 2 to 3 hours.[2,39] This refractory period can be used as a device to reduce the EIB response to exercise by utilising an exercise warm up period at intensity below 60% of maximal heart rate. A continuous exercise warm up of 15 minutes appears to be effective in reducing the EIB symptoms of subsequent exercise. This information is important to those individuals with EIB wishing to exercise at high levels. In addition, this fact requires consideration in the history of exercise before testing an individual for the diagnosis of EIB.

For the individual wishing to reduce EIB upon exercise, several steps can be taken. Firstly, climatic conditions must be considered. If the air is cold and dry, then a mask may provide protection from this irritant. A warm up of between 40 to 60% of maximum intensity for 15 minutes will provide some protection by eliciting a refractory period. These are typical mechanisms used to provide some relief from the symptoms of EIB associated with exercise.

4.1.1 Diet

The influence of diet on the severity of EIB has been little studied. However, there are emerging data with regard to the potential use of dietary modifications/supplementation for reducing decrements in pulmonary function associated with EIB.

Interestingly, one study has demonstrated a reduction in isocapnic hyperpnoea-induced bronchospasm with prior ingestion of caffeine.[59] In addition, Bara and Barley[60] reviewed several studies using caffeine in individuals with asthma. They concluded that caffeine has a modest effect on improving airways function in these individuals for about 4 hours. The suggestion would be that caffeine might reduce the severity of EIB however, this has not been further studied.

The potential role of antioxidant status in influencing the symptoms of EIB has begun to be investigated. Neuman et al.[61] supplemented the diet for 1 week with lycopene 30 mg/day to increase antioxidant status. Fifty-five percent of the participants with EIB were protected with this dose. Cohen et al.[2,39] gave 2g of ascorbic acid 1 hour before exercise in individuals with EIB. Nine of 20 participants demonstrated a protective effect of the ascorbic acid. These data suggest that improved antioxidant status may relieve some of the severity of EIB, although this concept requires further controlled studies. Finally, one study has investigated the potential for fish oil supplementation to reduce the severity of EIB,[62] although no relief of symptoms of EIB was demonstrated.

The dietary component most studied to-date with regard to altering severity of EIB is dietary sodium chloride. Burney[63] utilised epidemiological data that associated high salt consumption with markers for severity of asthma to develop the hypothesis that dietary salt consumption contributes to asthma morbidity and mortality. Recently, Gotshall and Mickleborough et al.,[4,64,65] performed a series of experiments to investigate the potential role for dietary salt as a modifier of the severity of EIB. In humans[4,65,66] elevation of dietary salt intake over 2 weeks exacerbated the decrements in FEV_1 measured post exercise, while dietary salt restriction over 2 weeks significantly improved EIB. Substituting sodium bicarbonate for sodium chloride supplementation demonstrated a protective effect of removing the chloride from salt. These data are summarised in figure 4. Dietary salt restriction improved post-exercise FEV_1 values to the least severe criteria for EIB, 10% reduction in FEV_1. The clinical relevance of these effects on EIB remains to be demonstrated.

In an initial attempt to investigate the possible mechanisms by which dietary salt might exacerbate EIB, Mickleborough et al.[64] used the guinea pig model for EIB, HIAO. This novel study demonstrated that increased salt consumption in guinea pigs worsened the HIAO response, and that blocking leukotriene production eliminated the HIAO response in both normal salt and high-salt guinea pigs. These data suggest that an intact leukotriene production and release system must be available for post-HIAO to occur in these guinea pigs. The interaction of dietary salt and leukotriene production and release in this model has yet to be determined.

In summary, dietary factors may well play a role in modifying the airway response to the hyperventilation of exercise. The most convincing data to-date are those implicating dietary salt in severity of EIB, and provide evidence for the use of dietary

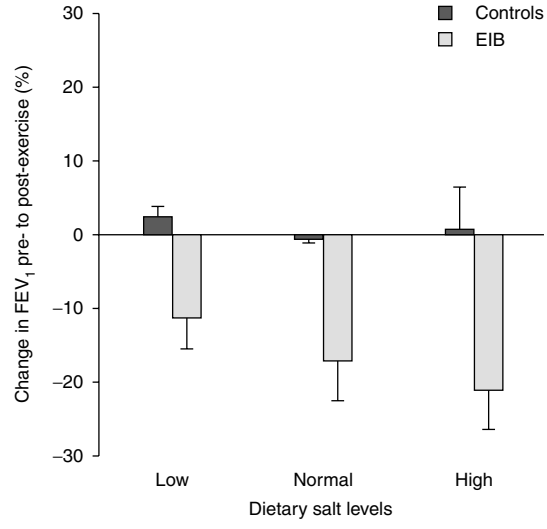

Fig. 4. Influence of dietary salt intake on severity of exercise-induced bronchospasm in individuals with exercise-induced bronchoconstriction (EIB).[4] **FEV_1** = forced expiratory volume in 1 second.

salt restriction as an nonpharmacological intervention to reduce the airways obstruction of EIB.

4.2 Pharmacological

Pharmacological treatment of EIB, shown in table III, is best determined sequentially. Individuals with asthma require control of their asthma before exercise. Subsequently, they may require specific treatment for asthma. Individuals without asthma typically just require treatment specifically for the EIB.

Inhaled β_2-adrenergic agonists are considered the first line therapy for preventing/treating EIB. Most athletes rely on short-acting β_2-agaonists inhaled 5 to 15 minutes before a period of exercise and for symptomatic relief after exercise. Ninety percent of those with EIB will have successful reduction in EIB with the prophylactic use of inhaled β_2-agonists.[67] Long-acting β_2-agonists, for example salmeterol, inhaled 30 to 60 minutes before exercise can have protection lasting up to 12 hours.[68] However, different β_2-agaonists may have to be tried to determine effectiveness. Gronnerod et al.[69] contrasted the effectiveness of two β_2-agonists, formoterol and terbutaline delivered via Turbuhaler to children with EIB. After two different doses of formoterol post-exercise reductions in FEV_1 were reduced to 5 to 8%. In contrast, FEV_1 fell 15 to 18% after terbutaline. Thus, formoterol typically demonstrated better effectiveness than terbutaline over 12 hours.

An alternative class of therapy to β_2-agonists includes sodium cromoglycate and nedocromil. Inhaled sodium cromoglycate and nedocromil are generally equivalent in modifying EIB mainly via prevention of mast cell mediator release.[70] Kelly et al.[71] reviewed clinical randomised controlled trials comparing nedocromil and sodium cromoglycate in treatment of EIB. There were no significant differences between these two treatments on EIB or on adverse effects. A meta-analysis of studies using nedocromil in individuals with EIB indicated an approximate 15% reduction in severity of EIB while reducing the post-exercise period of bronchoconstriction from about 30 to 10 minutes.[72]

Oral theophylline or inhaled anticholinergic therapy may also be considered if the above therapies are not successful. These fall into the category of bronchodilators. Some planning is required with these drugs, as they are not as fast acting as the β_2-agonists or sodium cromoglycate and nedocromil. Rapid-release theophylline can be taken 1 to 2 hours before exercise, while sustained release theophylline can be taken daily for prophylaxis. Inhaled anticholinergics need to be taken at least 30 minutes before exercise to have benefit. Theophylline may be used in combination with β_2-agonists for more complete protection.

Certain diuretics, when inhaled, have demonstrated effectiveness in EIB. Furosemide has been effective in several studies. For example, Munyard et al.[73] found that furosemide reduced the post-exercise decrease in FEV_1 in children with EIB to only 5%, compared with the decrease with placebo of 14.4%. Furosemide may have to be used with other drugs for more complete protection.[74] Novembre et al.[74] compared the effectiveness of furosemide to nedocromil alone and in combination. In children with EIB, post-exercise decreases in FEV_1 were 29, 15 and 11%, respectively, with placebo, nedocromil and furosemide. However, together the post exercise decrease in FEV_1 was only 5.75%. Therefore, while furosemide is often clinically effective, it may be beneficial to combine drug therapy to achieve more complete protection.

4.2.1 Anti-inflammatories

Anti-inflammatory treatment has been a long proven treatment for asthma and for EIB. However, both inhaled and oral anti-inflammatory treatments require planning with regard to exercise, as both require significant time to be effective. Thus, in terms of corticosteroid treatment, these drugs are typically used on a regular basis as maintenance/prophylaxis drugs. In addition, corticosteroids typically enhance the effectiveness of the β_2-agonists.[75] Corticosteroids are effective reducing the post exercise fall in FEV_1. For example, Hofstra et al.[76] found in children with EIB that

fluticasone propionate reduced the post exercise fall in FEV_1 from 34% to approximately 8%. However, some individuals are more resistant to corticosteroid therapy requiring combination therapy with the addition of other drugs, such as β_2-agonists, to control EIB.

Anti-Leukotriene Agents

Recently, leukotrienes have been implicated in EIB and the role of anti-leukotrienes in EIB has been widely studied.[41,42,77-82] In a multicentre trial of the comparative effectiveness of montelukast, an oral leukotriene antagonist, and the long-acting β_2-agonist, salmeterol, Edelman et al.[78] found that the EIB broncho-protective effect of montelukast was maintained throughout the 8 weeks of study. In contrast, a significant loss of bronchoprotection at weeks 4 and 8 was seen with salmeterol. At week 8, the percentage inhibition in the maximal percentage decrease in FEV_1 was 57.2 in the montelukast group and 33.0 in the salmeterol group. By week 8, 67% of patients receiving montelukast and 46% of patients receiving salmeterol had a maximal percentage decrease in FEV_1 of less than 20. Thus, long-term administration of montelukast provided consistent inhibition of EIB at the end of the 8-week dose administration period without tolerance. These data indicate that leukotriene antagonists were effective choices in the treatment of EIB.

Coreno et al.[83] contrasted the effectiveness of anti-leukotriene agents to a long-acting β_2-agonist. Specifically, they performed a random-order, blinded, double-dummy, placebo-controlled trial in 10 patients with EIB. Each participant received standard single doses of salmeterol, montelukast, zafirlukast, zileuton or placebo on separate days. The participants performed 4 minutes of cycle ergometry while breathing frigid air 1, 4, 8, and 12 hours after administration of the test agents. The primary endpoint was the extent of the decrement in the FEV_1 10 minutes after end of exertion. Salmeterol reduced the fall in FEV_1 from approximately 20 to 25% to approximately 5% over 8 hours post exercise. Montelukast and zafirlukast also offered long-lasting protection (not different from salmeterol), with no significant differences between them (montelukast, decrease in FEV_1 reduced to 9%; zafirlukast, decrease in FEV_1 reduced to 11% over 12 hours). Zileuton provided equivalent prophylaxis to salmeterol and the leukotriene antagonists for the first 4 hours, however, by 8 hours it was less effective than all the other active compounds and by 12 hours it did not differ from placebo. Therefore, the leukotriene receptor antagonists were equally as effective as salmeterol, but the leukotriene-synthesis inhibitor only had short-lived protection.

Vidal et al.[84] contrasted a leukotriene receptor antagonist montelukast with the corticosteroid budesonide in individuals with EIB. Twenty patients experienced both treatments separated by a 15-day washout period. Both the post-exercise decrease in FEV_1 and the post-exercise AUC (see section 3) were used as endpoints. Although the protection afforded by each drug varied between individuals, overall, budesonide provided superior protection to montelukast, particularly in the short-term. Both reduced the post-exercise decrease in FEV_1 to sub-clinical levels. However, because considerable individual differences in response occurred, patients need to be evaluated on the individual drug in order to determine the one most effective.

4.3 Summary

Both short-term and long-term β_2-agonists are effective medications in EIB and useful 'rescue' medications. The mast cell stabilisers, inhaled sodium cromoglycate and nedocromil, are also effective in some individuals. Theophylline, anticholinergic agents and furosemide can be effective alone or in combination therapy with other drugs. Anti-inflammatory drugs such as corticosteroids can be effective prophylaxis agents for individuals with EIB, although combination therapy may be required for more effective control of EIB. Recently, the anti-inflammatory agents that block leukotriene receptors or synthesis have demonstrated effectiveness in preventing EIB. All of these drugs, alone or in combination, have demonstrated the

ability to reduce EIB to sub-clinical levels. Importantly, individuals respond differently to the drugs available for treatment of EIB. Therefore, it is important to evaluate different drugs to determine the most effective one.

In contrast to pharmacological interventions for EIB, nonpharmacological interventions have not demonstrated the ability to improve EIB to subclinical levels. However, emerging research indicates that diet may be an important modifier of the severity of EIB and perhaps diet can be used to reduce the reliance on drugs or to reduce the dose of drug. This concept has not been investigated.

5. Perspective

EIB is prevalent in individuals with asthma and occurs in significant numbers of individuals without asthma. The presence of EIB in individuals with asthma interferes with regular exercise which could permit development of physical and metabolic fitness, relieving stress on pulmonary function. In addition, while many high-performing athletes experience asthma and have significant EIB, many pharmacological agents effective in the treatment of asthma and EIB are banned from use in those competing in sanctioned competitions (see table IV). The use of nonpharmacological interventions such as appropriate warm up and climatic conditions can help these athletes. The use of dietary modification for athletic competitors with EIB has not been examined. However, when treating an athlete, the potential for using a banned substance must be considered and the appropriate regulatory body contacted for the most current list of banned drugs.

While the stimulus and mechanism of EIB remains elusive, the data support the concept that hyperpnoea results in airways cooling and drying which triggers an inflammatory cascade. These inflammatory mediators are most likely to contribute to bronchoconstriction, although vascular engorgement, mucosal swelling and enhanced mucous production all probably contribute to the severity of airways obstruction. EIB is treatable, even in patients with highly reactive asthma and, therefore, exercise capacity can be enhanced in those with EIB.

It should be mentioned that individuals with EIB are potentially capable of very high athletic performance despite this condition. This is evident in the numbers of successful elite Olympic-calibre and world-class athletes who have EIB. Training, even to a high degree, is possible with this condition. However, caution should be taken with individuals with atopic asthma and other unfit individuals with EIB upon initiation of an exercise program. In a review of the effects of physical training in general in patients with asthma, Ram et al.[85] reviewed controlled clinical trials of training programmes in this patient population. Their review disclosed that physical training in individuals with asthma im-

Table IV. Medications approved or banned in international competition relevant to individuals with exercise-induced bronchoconstriction[a]

Approved	Banned
Inhaled medications:	Oral sympathomimetics/stimulants:
β_2-agonists	epinephrine
corticosteroids	ephedrine
sodium cromoglycate and nedocromil	pseudoephedrine
Theophylline	phenylephrine
Antihistamines	isoproterenol
Topical oxymetazoline and xylometazoline[b]	phenylpropanolamine
	isoetharine
	Oral β-agonists
	Oral and parenteral corticosteroids

a Anti-leukotriene agents had not been addressed at the time of this review.

b α-Adrenergic agonists.

proves cardiopulmonary fitness without changing lung function. No conclusion could be drawn as to the influence the training had on symptoms or to quality of life for the patient with asthma. Therefore, it would seem logical that with appropriate treatment of EIB, individuals can participate in regular physical activity and derive the usual benefits there from.

Acknowledgements

Portions of the data presented were collected with the assistance of a grant from the US Olympic Committee and US Swimming.

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