Review

Exercise Induced Bronchoconstriction:
A clinical approach

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SUMMARY. **Exercise-induced bronchoconstriction (EIB) describes the acute airway narrowing which occurs as a result of exercise. EIB commonly affects individuals with and without clinically recognized asthma, especially those who participate in competitive athletics. EIB is believed to be caused by the loss of water from the lower airways which is the result of heating and humidifying large volumes of air in a short period. The aforementioned procedure results in a hyperosmolar environment which activates various cellular mechanisms to release inflammatory mediators which in turn lead to airway smooth muscle contraction and bronchoconstriction. In elite athletes EIB may also develop from a process of airway injury and changes in the contractile properties of airway smooth muscle. Short acting β2-agonists are recommended first-line agents for pharmacologic treatment, although leukotriene receptor antagonists or inhaled corticosteroids with or without long-acting β2-agonists may be needed in refractory cases. If symptoms persist despite treatment, alternative diagnoses should be considered. In this review we summarize the pathophysiology, the clinical manifestations, the diagnostic approach and the treatment strategies of EIB.** ***Pneumon 2014, 27(2):139-146.***

INTRODUCTION

The term exercise-induced bronchoconstriction (EIB) is used to describe the transient and reversible narrowing of the lower airways that follows vigorous exercise, regardless of the presence or absence of clinically recognized asthma[1]. The term "exercise induced asthma" used in the previous years has now been replaced by the term "exercise induced bronchoconstriction". This change in the nomenclature of this condition seems to be accurate since exercise induced asthma refers tobronchospasm that occurs in patients with asthma when they exercise[2]; however, exercise induced bronchoconstriction can also occur in patients without underlying chronic asthma[3]. Thus, patients with exercise induced bronchoconstriction are patients who might not have evidence of asthma according to the current asthma guidelines,

have normal pulmonary function tests at rest, do not have any symptoms during their everyday physical activity, do not need to use β2-agonists other than with exercise and have a normal asthma control test (or other questionnaire used for the assessment of asthmatic symptoms)[2].

EIB occurs in approximately 90% of asthmatic subjects and in 40% of patients with allergic rhinitis[4]. Asthmatic patients with more severe or poorly controlled asthma are more likely to exhibit EIB than those with less severe or well-controlled disease[5]. In the general population the prevalence of EIB ranges from 7% to 20%[4]. Studies have shown that in elite-level athletes the prevalence of EIB varies between 30 and 70%, depending on the population studied, the type of sport, the environmental conditions and the methods implemented[4,6].

PATHOPHYSIOLOGY

Two main theories have been used to explain the mechanism of EIB: the thermal theory and the osmotic theory. The thermal theory, proposes that the cooling of the airway, which occurs as a result of water loss, causes vasoconstriction in bronchial vasculature. On rewarming, airway narrowing will occur due to the mechanical effects of vascular engorgement,vascular leakage, and edema of the airway wall.[1] Thus, in this scenario, airway narrowing would occur as a direct consequence of vascular events and would be unrelated to mediator release or airway smooth muscle contraction. On the other hand, the osmotic theory proposes that airway water loss results in increased osmolarity of the airway surface liquid, which extends to include the airway epithelial cells and submucosa. This hyperosmolar environment activates cellular mechanisms to release various mediators. These mediators, in turn, cause airway smooth muscle contraction and subsequent airway narrowing[1]. The aforementioned theories are summarized in Figure 1.

In elite athletes, the development of EIB seems to be caused by another mechanism, which includes airway injury and airway hyperresponsiveness. During intense physical activity conducted over prolonged amounts of time, the smaller airways are increasingly recruited in the humidification process. This process is repetitive during training and results in dehydration injury to the airway epithelium[1]. Epithelial repair of this airway injury involves microvascular leak and plasma exudation. Epithelial injury results in a reduced capacity to move water to the airway to respond to a hyperosmolar stimulus. With repeated injury, a larger airway surface area will need to be recruited in the conditioning process, thereby causing continued

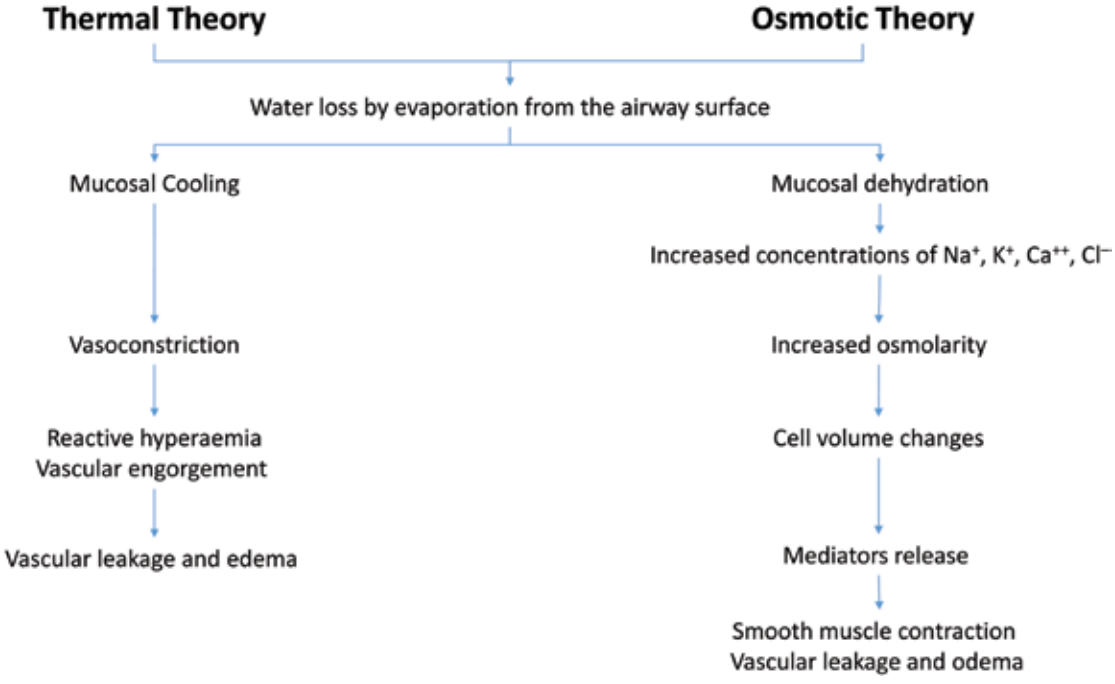

FIGURE 1. Pathophysiology of exercise induced bronchoconstriction.

progression of the airway injury[1]. This repeated exposure of airway smooth muscle cells to injury results in airway hyperresponsiveness in elite athletes. This airway hyperresponsiveness is reversible and does not occur any more when the athlete is out of season or after retirement.

DIAGNOSIS

Symptoms of EIB do not differ from those of usual asthma and include shortness of breath, cough, wheeze, and mucus production[3]. Atypical symptoms such as poor performance or feeling 'out of shape', abdominal pain, headache, muscle cramps, fatigue and dizziness may also occur[2]. Symptoms of EIB begin usually 6-8 min after strenuous exercise[7]. In some cases, patients recognize asthma symptoms during exercise and those symptoms continue to increase even after the intensity of exercise is reduced.

However, symptoms are neither sensitive nor specific and often are caused from vigorous exercise rather than EIB[8,9]. This is the reason why the diagnosis of EIB requires documentation of changes in lung function after exercise. It is important to point out that in a recent study only 35% of athletes reporting symptoms suggestive of EIB had objectively documented EIB after pulmonary function testing[8].

The diagnosis of EIB typically requires a decrease in forced expiratory volume in 1 second (FEV_1) at any 2 consecutive time points within 30 minutes after exercise of 10% to 15% of the pre-exercise FEV_1 value[6]. According to the ATS/ERS guidelines, FEV_1 is usually measured at 5, 10, 15, and 30 minutes after exercise, but may be more frequent if a severe response is expected[3]. However, there is no gold standard diagnostic procedure for the diagnosis of EIB and several tests can be used[9]. Diagnostic tests used for the diagnosis of EIB are summarized in Table 1.

Direct pharmacological challenge tests rely on the administration of agents (such as histamine and methacholine) which induce bronchoconstriction by acting directly on airway smooth muscle cells. Despite the fact that methacholine challenge testing is traditionally a very reliable test for the diagnosis of asthma, its role in the diagnosis of EIB is limited. Hence, a positive test does not specifically confirm EIB, whereas a negative test does not specifically exclude EIB[9]. Unlike direct challenge tests, indirect tests can accurately diagnose EIB[10], Indirect challenge tests include exercise challenge tests, eucapnic voluntary hyperpnea and inhalation of hyper osmolar aerosols (4.5% saline or dry powder mannitol)[3,10]. Although none of these tests are completely sensitive of specific for EIB, they are very useful for the identification of airway hyper responsiveness consistent with a diagnosis of EIB[3].

Exercise testing (either laboratory based i.e. treadmill cycle or ergometer) and field based testing (i.e. performing the sport activity) are very commonly used methods for the diagnosis of EIB[9]. During the exercise challenge test,

TABLE 1. Tests for the Diagnosis of Exercise-Induced Bronchoconstriction.

Indirect Tests	Advantages	Disadvantages
Eucapnic voluntary hyperpnea test	Sensitive and specific Less equipment needed	Need to monitor minute ventilation Relatively expensive
Field-based exercise challenge	Sensitive and specific for cold-weather athletes Minimal equipment Inexpensive	Not standardized Unable to control environment
Hypertonic saline test	Sensitive and specific Less equipment needed	Not as reliable if patient is treated with ICS
Laboratory-based exercise challenge	Sensitive and specific Standardized	Monitor heart rate and minute ventilation Relatively expensive
Direct Tests		
Methacholine challenge	Less equipment needed Standardized	Low Specificity
Histamine challenge	Less equipment needed Standardized	Low Specificity

ICS: Inhaled Corticosteroids

the patient undergoes a rapid increase in exercise intensity over approximately 2–4 minutes in order to achieve a high level of ventilation. Most protocols recommend breathing dry air (10 mg H_2O/L) with a nose clip in place while running or cycling at a load sufficient to raise the heart rate to 80–90% of predicted maximum or ventilation to reach 17.5–21 times FEV_1. Once this level of exercise is achieved, the subject should continue exercise at that high level for an additional 4–6 minutes. These targets are more rapidly achieved with running exercise compared with cycling[3]. FEV_1 is measured at baseline and at several time points after the exercise stimulus. One of the main limitations of this method is the failure to increase the exercise load to the needed level that will trigger the development of EIB[9]. Furthermore, during the field based tests, the workload and environmental conditions are difficult to control and measure and this might lead in false negative results[9].

Eucapnic voluntary hyperventilation testing involves hyperventilation of a gas mixture of 5% carbon dioxide and 21% oxygen at a target of ventilation of 85% of the patient's MVV[11]. This hyperventilation procedure continues for 6 min and FEV_1 measurements are performed in specific intervals up to 20 min after the test and are compared to baseline[11]. Eucapnic voluntary hyperventilation testing has a high sensitivity to identify EIB and a high negative predictive value[9]. The major limitation of this method is that it required special equipment which is not widely available and might be expensive.

Mannitol and hypertonic saline (4.5% NaCl) inhalation are examples of osmotic challenge tests for the documentation of EIB. As a diagnostic tool, mannitol inhalation compares well with EVH and exercise testing[12-14]. Mannitol, is commercially available as a convenient and standardized test kit with prefilled dry powder capsules and single-use dry powder inhaler devices, which are portable[15]. This is a significant advantage over other bronchoprovocation techniques that require expensive equipment that is not portable.

Regarding the results in the indirect challenge testing, the severity of EIB can be graded as mild, moderate, or severe if the percent fall in FEV_1 from pre-exercise level is >10% but ≤25%, >25% but ≤50%, or >50%, respectively[3]. In case the patient receives medications for the treatment of asthma or rhinitis,the drugs should be withheld. The recommended times of drug withholding are presented in Table 2[16].

Differential diagnosis of EIB includes several diseases such as anxiety disorders, cardiac diseases (e.g. congestive heart failure, coronary artery disease, dysrhythmias, hypertrophic cardiomyopathy, valvular abnormalities etc.), deconditioning, obesity, hyperventilation syndrome, myopathies, pulmonary arteriovenus malformations, pulmonary disease (e.g. chronic asthma, chronic obstructive pulmonary disease, cystic fibrosis, interstitial lung disease, pectusexcavatum, scoliosis, tracheobronchiolar malacia, and vocal cord dysfunction[10,17]. The differential diagnosis has to be always examined especially when bronchial provocation testing results are normal[10].

A diagnostic algorithm for the evaluation of patients with suspected EIB is shown in Figure 2.

TABLE 2. Minimum time intervals from last dose to the test performance

Medication	Time to withhold
Inhaled non-steroidal anti-inflammatory agents (e.g. sodium cromoglycate, nedocromil sodium)	8 hours
Short acting β2-agonists (e.g salbutamol, terbutaline)	8 hours
Inhaled corticosteroids	12 hours
Ipratropium bromide	12-24 hours
Long acting β2-agonists	24 hours
Theophylline	24 hours
Tiotropium bromide	7 days
Antihistamines (e.g. cetirizine, fexofenadine, loratadine)	72 hours
Leukotriene- receptor antagonists (e.g. montelukast sodium)	4 days

Coffee, tea, cola drinks, chocolate or other food containing caffeine should be withheld on the day of the test.
Vigorous exercise should not be performed prior to testing on the day of the test
Patients should refrain from smoking for at least 6 hours prior to testing.
Modified from[16]

TREATMENT

EIB affects many aspects of a patient's life, and is a very important problem in athletes regardless of the severity of symptoms. Although EIB is usually mild or moderate, deaths have been also reported. The main goal of treatment is not only to ensure that the patient will exercise safely but also to help athletes of all levels to maximize their performance during athletic competitions[10].

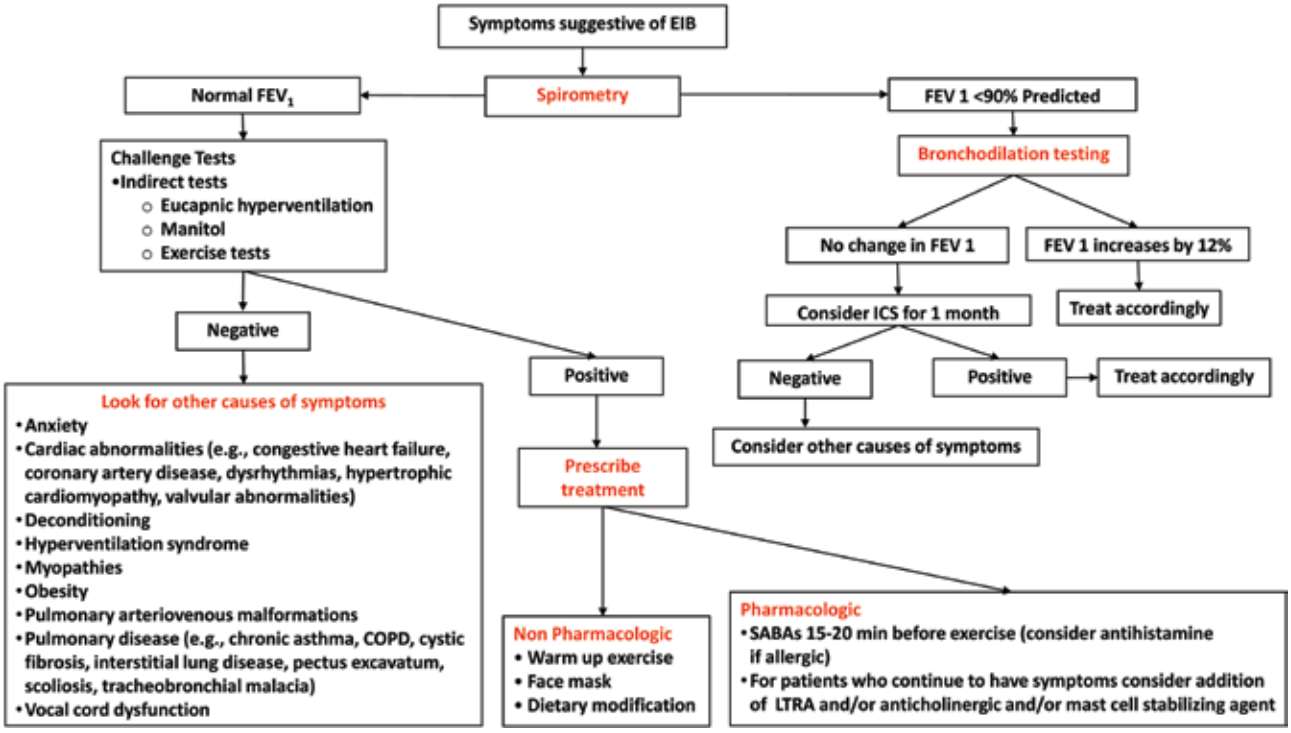

FIGURE 2. Diagnostic and therapeutic algorithm for exercise induced bronchoconstriction.

The treatment of EIB can be divided in two major categories the non-pharmacologic treatment and the pharmacologic treatment. Non pharmacologic options for the management of EIB include pre-exercise warm up, the use of heat exchange masks and nutritional methods. Typically, the pre-exercise warm-up consists of 10–15 minutes of moderately vigorous exercise, and subsequent EIB is reduced for the next 2 hours, resulting in a so-called "refractory period"[3]. Although various approaches of pre exercise warm up have been tried, including low-intensity, high-intensity, interval, or continuous exercise, and combinations of these, this intervention has not been provento be effective in elite athletes, especially those exercising in cold water[10].

Heat exchange masks are used to limit cold air exposure during exercise in athletes with EIB. These masks are commercially available, however, their use does not seem to be as effective as pre-treatment with salbutamol in the prevention of bronchoconstriction and sometimes are not practical to be used during competition[10,18].

Nutritional changes seem to reduce EIB. However, long term studies are lacking. The most important dietary intervention seems to be the intake of high dose of omega 3 fish oil supplementation. A recent study has shown that high dose omega 3 fish oil supplementation for three weeks not only reduced the use of bronchodilators in the treatment group, but also resulted in a reduction of specific inflammatory biomarkers, including plasma LTB4, TNF-α and IL1β levels[19]. A second study has compared the effectiveness of fish oil to montelukast and has shown that both interventions had similar effects in the prevention of EIB and the combination of fish oil with montelukast did not confer a greater protective effect than either intervention alone[20]. The potential antiinflammatory effect of omega 3 fish oil supplementation stems from its active ingredient, eicosapentaenoic acid, which is a competitive substrate with arachidonic acid for the generation of inflammatory mediators. The derivatives of arachidonic acid are LTB4, a potent neutrophil chemoattractant, and proinflammatory mediator, and the cysteinyl series of Leucotriens (LTC4, LTD4, and LTE4), which produce potent smooth musclecontraction and bronchoconstriction[21]. Arachidonic acid is the progenitor of LTB4 via the 5-lipoxygenase enzymatic pathway. Eicosapentaenoics acid, can inhibit Arachidonic acid metabolism competitively via these enzymatic pathways and, thus, can suppress production of the n-6 eicosanoid mediators. Thus, increasing dietary ω-3 fats can shift the balance of the eicosanoids

produced to a less inflammatory mixture by reducing the production of proinflammatory Leucotriens[19]

Pharmacologic therapy is the most effective treatment for EIB and includes short-acting β2-agonists (SABAs), long-acting β2-agonists (LABAs), leukotriene receptor antagonists (LTRAs), and inhaled corticosteroids (ICSs). In the past mast cell stabilizing agents have been also used although today there agents are not preferred. Inhaled anticholinergic agents (such as ipratropium) and antihistamines, might play a minor role in treating some patients with EIB.

Short acting β2-agonists (such as salbutamol) are recommended as first line treatment both as prevention and for the relief of acute symptoms. They should be administered shortly before exercise (approximately 15 min) since they have a peak action in 15-60 min which lasts approximately 4 hours[10]. These agents work by stimulating β2-receptors on airway smooth muscle, causing muscle relaxation and bronchodilation as well as possibly preventing mast cell degranulation. However, short acting β2-agonists may fail to prevent bronchoconstriction in 15–20% of patients with asthma. Furthermore, daily use of short acting β2-agonists leads to tolerance, due to desensitization of the β2-receptors on mast cells and airway smooth muscle,and this tolerance is manifested as a reduction in duration of protection against EIB, and a prolongation of recovery in response to SABA after exercise[3]. This is the reason why it is recommended that short acting β2-agonists should be used in less than daily on average for the prevention of EIB. Patients who use SABAs on a more regular basis (e.g., daily) should be preferably treated with a controller agent, such as ICS or LTRAs[3].

Long acting β2-agonists have also been shown to be effective for the prevention of EIB; however, according to the asthma management guidelines, it is recommended that they should not be used unless there is a concomitant use of a controller medication, such as inhaled corticosteroids (ICS). Concurrent use of ICS plus long acting β2-agonists has also been shown to be effective and superior to use of ICS alone in managing EIB[10].

Mast cell stabilizers such as cromolyn sodium and nedocromil sodium when inhaled shortly before exercise attenuate EIB but their duration of action is short (1-2 hours). They do not have a bronchodilator activity. They may be effective alone or as added therapy with other drugs for EIB[5]. Long-term use of either drug is not accompanied by tolerance. Furthermore, these drugs have excellent safety profiles which in combination with their rapidity of action, results to their validity to attenuate EIB in responsive individuals[5]. However, these drugs are not considered first-line options for the management of EIB today.

EIB which occurs in asthmatic patients is controlled by maintenance anti-inflammatory treatment either alone or in combination with other short-term preventive treatment. ICS use in asthma has been also associated with attenuation of hyper responsiveness to direct and indirect stimuli, including exercise. The effect of ICS on EIB seems to be dose and time dependent and may be associated with decreases in inflammatory mediators[5]. This bronchoprotective effect of ICS begins approximately 4 hours after the first dose and reaches a plateau after 1 week of long-term therapy. ICS can be also used in combination with adrenergic agonists or leukotriene receptor antagonists. However, it is important to state that inhaled corticosteroid therapy does not prevent the occurrence of tolerance from daily use of β2-agonists.

A recent study has shown that in asthmatic patients with mild asthma who experienced EIB, the use of the fixed combination of formoterol and budesonide (6/200μg) given as needed was superior from the as needed use of terbutaline (a short acting β-agonist) alone and was equally effective with the everyday use of budesonide alone. The authors also conclude that except of this non inferiority in the use of as needed combination compared to the ICS alone, patients were also receiving lower doses of ICS which might be related to fewer adverse events caused by the ICS[22].

Leucotriene receptor antagonists have been shown to have a persistent benefit against EIB. Montelukast has an onset of action within 2 hours and continues to have a preventive benefit for up to 24 hours after a single oral dose[10]. When used daily does not result to tolerance and can be used for intermittent or maintenance prophylaxis. However, it provides protection that may not be complete and although it has been shown to accelerate the time to recovery from EIB when it occurs, it has no use to reverse airway obstruction[5]. Finally short acting β2-agonists have been shown to be more effective than montelukast in the prevention of EIB[10].

Anticholinergics provide some protection against EIB but are not as effective as short acting β2-agonists or leukotriene receptor antagonists[10]. Furthermore, not all patients appear to respond to anticholinergic agents, and responsiveness may be variable in the same patient[5]. Finally, antihistamines can be used as additional therapy in patients with EIB who have allergies and continue to have symptoms despite using an inhaled short acting

TABLE 3. Treatment of Exercise-Induced Bronchoconstriction.

Pharmacologic Therapy

- Administration of an inhaled short-acting β2-agonist (SABA) 15 minutes before exercise.
- Addition of a controller agent whenever SABA therapy is used daily or more frequently.
- For patients with EIB who continue to have symptoms despite using an inhaled SABA, or who require an inhaled SABA daily or more frequently:
  - The guidelines **recommend against** daily use of an inhaled long acting β2-agonist as single therapy
  - It is recommend daily administration of an inhaled corticosteroid (**but** notonly before exercise)
  - Administration of a leukotriene receptor antagonist
  - Administration of a mast cell stabilizing agent before exercise
  - Administration of an inhaled anticholinergic agent before exercise
- For patients with EIB and allergies who continue to have symptoms despite using an inhaled SABA before exercise, administration of an antihistamine is suggested

Non Pharmacologic Therapy

- Warm-up exercise before planned exercise
- When exercising in cold weather, it is recommended routine use of a device (i.e., mask) that warms and humidifies the air during exercise
- For patients with EIB who have an interest in dietary modification to control their symptoms it is recommended
  - implementation of a low-salt diet
  - dietary supplementation with fish oils
  - dietary supplementation with ascorbic acid
  - but **against** dietary supplementation with lycopene

β2-agonist before exercise[3]. Therapeutic interventions for the prevention of EIB are shown in Table 3.

CONCLUSION

EIB commonly affects individuals with and without asthma, and is very often in elite athletes. The initial stimulus for EIB stems from airway water loss that occurs when the lower airways must condition large volume sof air in a short period. The resulting hyperosmolar environmentactivates various cellular mechanisms to release numerous mediators,which, in turn, lead to airway smooth muscle contraction and bronchoconstriction. Symptoms are not specific and diagnostic confirmation is necessary preferably using indirect challenge tests. Short acting β2-agonists are recommended first-line agents for pharmacologic treatment, although leukotriene receptor antagonists or inhaled corticosteroids with or without long-acting β2-agonists may be needed in refractory cases. Better understanding of the mechanisms of EIB would help in its more efficient treatment.

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